FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
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U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	
09/926641	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/03334	24 May 2000	28 May 1999

TITLE OF INVENTION

AGENT FOR EXPRESSION OF LONG-TERM POTENTIATION OF SYNAPTIC TRANSMISSION COMPRISING COMPOUND HAVING BRAIN SOMATOSTATIN ACTIVATION PROPERTY

APPLICANT(S) FOR DO/EO/US

MATSUOKA Nobuya et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Request for Priority Under 35 U.S.C. 120
PCT/IB/308
PCT/IB/304

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926641	PCT/JP00/03334	215869US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =	0	x $18.00	**$0.00**
Independent claims	- 3 =	0	x $84.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
		TOTAL OF ABOVE CALCULATIONS =		**$890.00**
☐	Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.			**$0.00**
		SUBTOTAL =		**$890.00**
	Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +			**$0.00**
		TOTAL NATIONAL FEE =		**$890.00**
☐	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			**$0.00**
		TOTAL FEES ENCLOSED =		**$890.00**
		Amount to be: refunded		$
		charged		$

a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Nov. 28 2001
DATE

09926641
PCT/JP00/03334
Rec'd PCT/PTO 28 NOV 2001

DESCRIPTION

AGENT FOR EXPRESSION OF LONG-TERM POTENTIATION OF SYNAPTIC TRANSMISSION COMPRISING COMPOUND HAVING BRAIN SOMATOSTATIN ACTIVATION PROPERTY

Technical Field

The present invention relates to an agent for the expression of long-term potentiation of synaptic transmission, an anti-dementia agent and an anti-amnesia agent, all of which containing a compound having a brain somatostatin activation property. More particularly, the present invention relates to an agent for the expression of long-term potentiation of synaptic transmission, an anti-dementia agent and an anti-amnesia agent, all of which containing a compound exerting a brain somatostatin release promoting action through suppression of the negative feedback mechanism of brain somatostatin release. The present invention moreover relates to a method for expressing long-term potentiation of synaptic transmission, a method for the treatment and/or prophylaxis of dementia and amnesia, and a screening method of these drugs using a somatostatin releasing property as an index.

Background Art

The hippocampal function is said to be responsible for learning and memory. When an input neuron of the hippocampus is stimulated for a short time at high frequency, the efficiency of synaptic transmission continues to increase for a long time thereafter. This phenomenon is called long-term potentiation (hereinafter also referred to as LTP) of synaptic transmission, and has been recognized as a cellular model of learning and memory (T. V. P. Bliss and G. L. Collingridge, Nature vol. 361, p. 31, 1993). There is a demand for further elucidation of the mechanism of the LTP and the relation thereof with learning and memory. Also, a search for a compound having a property of long-term potentiation of synaptic transmission has been desired.

Somatostatin has been known for quite a long time as a hypothalamic hormone capable of suppressing the secretion of somatotropin from the pituitary gland. It has been recently found that it is also present in the cerebral cortex and the hippocampus, that are important cerebral sites for memory and learning, at high concentrations, playing an important role in memory and learning as a neuromodulator.

Disclosure of the Invention

As a result of the intensive studies of the present inventors,

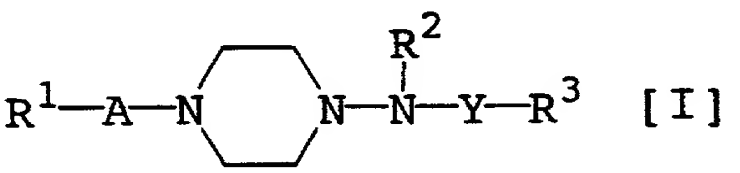
it has been newly found that a compound having a brain somatostatin release promotion property expresses long-term potentiation of synaptic transmission. Based on this new finding, the inventors have found that administration of a compound having a brain somatostatin release promoting property leads to the prophylaxis and/or treatment of cerebral diseases such as dementia, amnesia, manic-depressive psychosis, schizophrenia, Parkinson's disease, psychosomatic disease, and the like, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) An agent for expression of long-term potentiation of synaptic transmission, which comprises a compound having a brain somatostatin activation property as an active ingredient;
a method for expressing long-term potentiation of synaptic transmission, comprising administering an effective amount of a compound having a brain somatostatin activation property;
use of a compound having a brain somatostatin activation property for the production of an agent for the expression of long-term potentiation of synaptic transmission; and
a pharmaceutical composition for expression of long-term potentiation of synaptic transmission, which comprises a compound having a brain somatostatin activation property, and a pharmaceutically acceptable carrier or excipient.

(2) The agent, the method, the use and the pharmaceutical composition of (1), wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

(3) The agent, the method, the use and the pharmaceutical composition of (1) or (2), wherein the compound has the following formula [I]:



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which

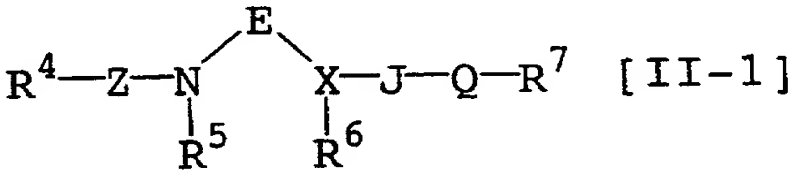
may be substituted with halogen,

A is -CO-, -SO_2- or lower alkylene, and

Y is -CO-, -SO_2- or -CONH-,

or pharmaceutically acceptable salts thereof.

(4) The agent, the method, the use and the pharmaceutical composition of (1) or (2), wherein the compound has the following formula [II-1]:



[II-1]

wherein

R^4 is acyl,

R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or -SO_2-,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

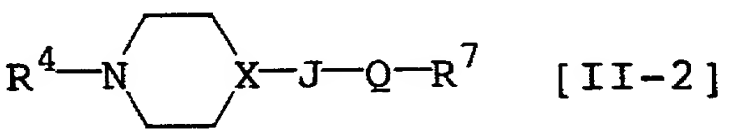
Q is -CH_2-, -CO-, -SO_2- or -N=CH-, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, $-CO-$ or $-SO_2-$, or
2) J is lower alkylene,
or pharmaceutically acceptable salts thereof.

(5) The agent, the method, the use and the pharmaceutical composition of (1) or (2), wherein the compound has the following formula [II-2]:



[II-2]

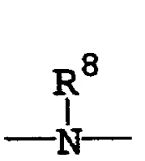
wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or



wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

(6) The agent, the method and the pharmaceutical composition of any of (1) to (5), which is for the prophylaxis and/or treatment of cerebral diseases; and the use according to any of (1) to (5), which is for the production of an agent for the prophylaxis and/or treatment of cerebral diseases.

(7) The agent, the method and the pharmaceutical composition of (6), which is for the prophylaxis and/or treatment of dementia or amnesia; and the use according to (6), which is for the production of an agent for the prophylaxis and/or treatment of dementia or amnesia.

(8) A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises using a somatostatin releasing action as an index.

(9) The screening method of (8), which is a screening method of an

anti-dementia agent or anti-amnesia agent.

(10) A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises stimulating hippocampal slices, bringing a hippocampal slice into contact with a test compound, measuring an amount of somatostatin released from the hippocampal slice and/or a release time thereof, measuring an amount of somatostatin released from a hippocampal slice and/or a release time thereof in the absence of a contact with the test compound, and comparing the amounts and/or the times to calculate the amount of somatostatin released from the hippocampal slice and/or the release time thereof caused by the contact with the test compound.

(11) The screening method according to (10), which is a screening method of an anti-dementia agent or anti-amnesia agent.

(12) The agent, the method, the use and the pharmaceutical composition according to (1), wherein the compound having the brain somatostatin activation property is obtained by the screening method of any of (8) to (11).

(13) A commercial package comprising the pharmaceutical composition for expression of long-term potentiation of synaptic transmission of any of (1) - (7), (12) and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition can or should be used for expression of long-term potentiation of synaptic transmission.

(14) A compound selected by the screening method described in any of (8) to (11).

Brief Description of the Drawing

Fig. 1 is a bar graph showing the action of compound 1 to be mentioned later, i.e., N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate, on somatostatin release from rat hippocampal slice upon stimulation with 50mM K^+, wherein the axis of ordinate is somatostatin release (%) and each value is mean±S.E.M (n=10 - 11). The symbol * means that Dunnett's multiple comparison test showed a significant difference by $P<0.05$ of the group containing various concentrations of compound 1 as compared to the control group.

Fig. 2 is a bar graph showing the action of compound 1 on hippocampus long-term potentiation phenomenon, wherein the axis of ordinate shows the magnitude of LTP by the integral (%·min) of potential variation (%) from 12 minutes to 62 minutes after tetanic stimulation. The symbol

* means that one-way analysis of variance and Dunnett's multiple comparison test showed a significant difference by $P<0.05$ of the group containing various concentrations of compound 1 as compared to the control group. The symbol ** means that one-way analysis of variance and Dunnett's multiple comparison test showed a significant difference by $P<0.01$ of the group containing various concentrations of compound 1 as compared to the control group.

Fig. 3 is a bar graph showing the dose-response dependency of compound 1 with regard to voltage-dependent calcium channel, wherein the axis of ordinate shows variation (%) of the maximal value of the membrane potential dependent calcium current to the value before the addition of compound 1, wherein each value is mean$\pm$S.E.M (n=7). The symbol * means that Dunnett's multiple comparison test showed a significant difference by $P<0.05$ of the group containing various concentrations of compound 1 as compared to the control group. The symbol ** means that Dunnett's multiple comparison test showed a significant difference by $P<0.01$ of the group containing various concentrations of compound 1 as compared to the control group.

Fig. 4 is a bar graph showing the action of somatostatin and compound 1 on the membrane potential dependent calcium current, wherein the axis of ordinate shows variation (%) of the maximal value of the membrane potential dependent calcium current upon addition of somatostatin alone or both compound 1 and somatostatin, to the value before addition of somatostatin (10^{-7} M) alone or both compound 1 (10^{-7} M) and somatostatin (10^{-7} M) and each value is mean$\pm$S.E.M., and the numerals in parentheses are the number of times of measurements. The symbol ** means that Dunnett's multiple comparison test showed a significant difference by $P<0.01$ of the group containing compound 1 and somatostatin as compared to the group containing somatostatin.

Detailed Description of the Invention

Respective definitions and specific examples thereof used in the present invention, as well as preferable embodiments thereof are explained in detail in the following.

Compound having brain somatostatin activation property

The activation property of brain somatostatin means, for example, an action to promote release of brain somatostatin, an action to increase biosynthesis of somatostatin within nerve cells, an action to activate somatostatin receptors, an action to potentiate expression of

somatostatin property, an action to potentiate somatostatin signal transduction and the like.

The compound to be used in the present invention is one capable of activating brain somatostatin based on at least one of the aforementioned properties. Particularly, a compound having a brain somatostatin release promoting property is preferably used, which is preferably a compound that shows a brain somatostatin release promoting property through suppression of the negative feedback mechanism of brain somatostatin release.

Examples of promotion of release of brain somatostatin include actions of, for example, suppression of a negative feedback mechanism of brain somatostatin release, release of suppression by somatostatin of voltage-dependent calcium channel present in neuron, promotion of the voltage-dependent calcium channel, modification of mutual intracellular action between G protein and calcium channel, phosphorylation of calcium channel, modification of K^+ channel, influencing kinetic behavior of somatostatin-containing vesicle, and the like, whereby release of somatostatin is promoted.

The action to increase biosynthesis of somatostatin in the nerve cells may be, for example, an action to potentiate the expression of somatostatin mRNA, an action to promote protein synthesis from mRNA, or an action to promote cleaving out from the precursor of somatostatin, wherein these actions promote the release of brain somatostatin.

The brain somatostatin release promoting property is evaluated by the method to be mentioned later.

The action to activate somatostatin receptors may be, for example, the actions to stimulate somatostatin receptors, to suppress desensitization of somatostatin receptors, to suppress intracellular transfer of somatostatin receptors, to increase the number of somatostatin receptors present in the postsynaptic membrane and the like.

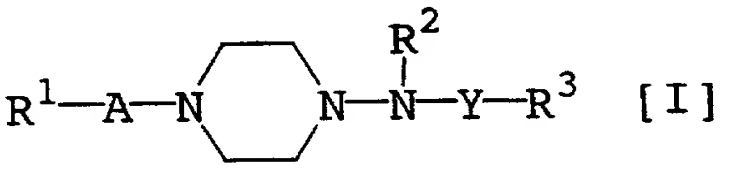
The action to potentiate the expression of somatostatin property may be, for example, an action to suppress the decomposition of somatostatin, an action to suppress the re-uptake of somatostatin and the like.

The action to potentiate the signal transmission of somatostatin is exemplified by an action to potentiate G protein, cAMP, protein kinase, protein phosphatase, transcription factor and the like, coupled

with a somatostatin receptor, wherein the action is directed to an intracellular signal transduction messenger and the like other than somatostatin receptor, thereby to potentiate the signal transduction of somatostatin.

The compound having a brain somatostatin activation property to be used in the present invention encompasses any compound having such an activation property. Preferable examples thereof include compounds of the following formulas:

① formula [I]



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

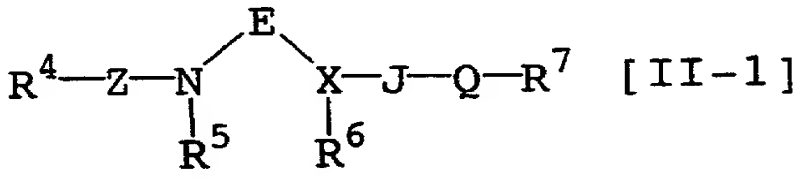
R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, $-SO_2-$ or lower alkylene, and

Y is -CO-, $-SO_2-$ or -CONH-

(EP Publication No. 436734) (hereinafter also referred to as compound [I]), and pharmaceutically acceptable salts thereof and

② formula [II-1]:



[II-1]

wherein

R^4 is acyl,

R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with

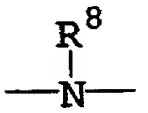
a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or $-SO_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or



wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

Q is $-CH_2-$, -CO-, $-SO_2-$ or -N=CH-, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or $-SO_2-$, or

2) J is lower alkylene,

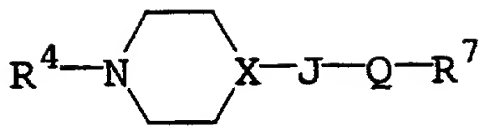
(hereinafter also referred to as compound [II-1]) and pharmaceutically acceptable salts thereof.

Preferred compound [I] is one which has a lower alkyl, phenyl, naphthyl or thienyl for R^1, hydrogen or lower alkyl for R^2, phenyl which may be substituted with a halogen for R^3, -CO- for A, and -CO- or $-SO_2-$ for Y.

More preferred compound [I] is one which has a lower alkyl for R^1, hydrogen for R^2, phenyl which is substituted with a halogen for R^3, -CO- for A, and -CO- for Y.

Most preferred compound [I] is N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate (compound 1) (International Publication No. WO98/25914).

When Z is a single bond, E is ethylene, and R^5 and R^6 are taken together to form ethylene, preferable compounds [II-1] can be represented by the following general formula [II-2]:



[II-2]

wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, (hereinafter also referred to as compound [II-2]) and pharmaceutically acceptable salts thereof.

Preferred compound [II-2] is one which has lower alkanoyl, esterified carboxy, substituted or unsubstituted aroyl, lower alkylsulfonyl, substituted or unsubstituted arylsulfonyl, or cyclo(lower)alkylcarbonyl for R^4, and aryl or arylamino, each aryl of which may be substituted with halogen for R^7, CH or N for X, a single bond, lower alkylene or

(wherein R^8 is hydrogen, lower alkyl or an N-protective group) for J, and $-CH_2-$, $-CO-$ or $-SO_2-$ for Q,

provided that when X is N, then J is a single bond or lower alkylene, and pharmaceutically acceptable salts thereof.

More preferred compound [II-2] is one which has lower alkanoyl, lower alkoxycarbonyl, aroyl, aroyl substituted with

halo(lower)alkoxy, lower alkylsulfonyl, arylsulfonyl, arylsulfonyl substituted with halogen, or cyclo(lower)alkylcarbonyl for R^4, aryl or arylamino, each aryl of which may be substituted with halogen for R^7, CH for X, a single bond or -NH- for J, and -CO- or $-SO_2-$ for Q, and pharmaceutically acceptable salts thereof.

Particularly more preferred compound [II-2] is one which has lower alkanoyl, lower alkoxycarbonyl, aroyl, aroyl substituted with halo(lower)alkoxy, lower alkylsulfonyl, arylsulfonyl, arylsulfonyl substituted with halogen, or cyclo(lower)alkylcarbonyl for R^4, aryl or arylamino, each aryl of which may be substituted with halogen for R^7, CH for X, -NH- for J, and -CO- for Q,
and pharmaceutically acceptable salts thereof.

Most preferred compound [II-2] is one selected from the group consisting of
N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide,
N-(1-acetylpiperidin-4-yl)-N'-(4-fluorophenyl)urea,
4-(4-fluorobenzoylamino)-1-methoxycarbonylpiperidine,
4-(4-fluorobenzoylamino)-1-(4-fluorophenylsulfonyl)piperidine,
4-(4-fluorobenzoylamino)-1-(4-trifluoromethoxybenzoyl)piperidine,
4-(4-fluorobenzoylamino)-1-methylsulfonylpiperidine,
N-(1-methoxycarbonylpiperidin-4-yl)-N'-(4-fluorophenyl)urea,
N-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)-N'-(4-fluorophenyl)-urea,
N-(1-benzoylpiperidin-4-yl)-4-fluorobenzamide,
N-(1-pivaloylpiperidin-4-yl)-4-fluorobenzamide and
N-(1-cyclopropylcarbonylpiperidin-4-yl)-4-flurobenzamide.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the terms "lower alkenyl", "lower alkenyloxy", "lower alkenylamino", "lower alkynyl", "lower alkynyloxy" and "lower alkynylamino" is intended to mean a group having 2 to 6 carbon atoms.

The lower moiety in the terms "cyclo(lower)alkyl", "cyclo(lower)alkyloxy" and "cyclo(lower)alkylamino" is intended to mean a group having 3 to 6 carbon atoms.

Suitable "lower alkyl" and lower alkyl moiety in the terms "substituted-lower alkyl", "ar(lower)alkyl", "halo(lower)alkyl", "lower alkylamino", "lower alkylsilyl", "lower alkylthio" and "lower alkylsulfonyl" may be a straight or branched C_1-C_6 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, ethylpropyl, hexyl or the like, in which preferable on is methyl.

Suitable "lower alkenyl" and lower alkenyl moiety in the terms "lower alkenyloxy" and "lower alkenylamino" may be a straight or branched C_2-C_6 alkenyl such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, isopropenyl, butadienyl, pentadienyl, hexadienyl or the like, in which preferable one is ethenyl, propentyl or butadienyl.

Suitable "lower alkynyl" and lower alkynyl moiety in the terms "lower alkynyloxy" and "lower alkynylamino" may be a straight or branched C_2-C_6 alkynyl such as ethynyl, propargyl, butynyl or the like, in which preferable one is ethynyl.

Suitable "cyclo(lower)alkyl" and cyclo(lower)alkyl moiety in the terms "cyclo(lower)alkyloxy" and "cyclo(lower)alkylamino" may be cyclo(C_3-C_6)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in which preferable one in the definitions of general formulas [II-1] and [II-2]is cyclopropyl.

Suitable "aryl" in the definitions of general formula [I] may be phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl, and the like, in which preferable one is phenyl or naphthyl.

Suitable "ar(lower)alkoxy" in the definitions of general formula [I] may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy, trityloxy and the like.

Suitable "aryl" and aryl or ar moiety in the terms "ar(lower)alkoxy", "aryloxy", "arylamino", "arylsulfonyl", "aroyl" and "ar(lower)alkyl" in the definitions of general formulas [II-1] and [II-2] may be phenyl, naphthyl, phenyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl or tolyl.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, phenylpropyl, benzhydryl, trityl and the like, in which preferable one in the definitions of general formulas [II-1] and [II-2] is benzyl.

Suitable "lower alkylene" in the definitions of general formula [I] may be methylene, ethylene, propylene, pentamethylene, hexamethylene, and the like.

Suitable "lower alkylene" and lower alkylene moiety in the term "lower alkylenedioxy" in the definitions of general formulas [II-1] and [II-2] may be a straight or branched C_1-C_6 alkylene such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, ethylethylene or the like, in which preferable one is methylene, ethylene or trimethylene.

Suitable "lower alkoxy" and lower alkoxy moiety in the terms "ar(lower)alkoxy" and "halo(lower)alkoxy" may be a straight or branched C_1-C_6 alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, methylpropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is methoxy or tert-butoxy.

Suitable "heterocyclic group" in the definitions of general formula [I] may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom. The preferred examples of thus defined "heterocyclic group" may be

unsaturated, 3 to 8-membered, more preferably 5 or 6-memebered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;
unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;
unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, etc.;
unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the like.

The above-mentioned "lower alkyl", "aryl", "ar(lower)alkoxy", "heterocyclic group", "cyclo(lower)alkyl" and "ar(lower)alkyl" in the definitions of general formula [I] may be substituted with halogen [e.g. fluorine, chlorine, bromine and iodine].

Suitable "halogen" and halo moiety in the term "halo(lower)alkyl" may be fluorine, chlorine, bromine and iodine, in which preferable one is fluorine, chlorine or iodine.

Suitable "halo(lower)alkyl" may be lower alkyl substituted with one or more halogens such as chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentachloroethyl or the like, in which preferable one is trifluoromethyl.

Suitable "halo(lower)alkoxy" may be lower alkoxy substituted with one or more halogens such as chloromethoxy, dichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, pentachloromethoxy or the like, in which preferable one is trifluoromethoxy.

Suitable "lower alkylamino" may be mono or di(lower)alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, isobutylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, diisopropylamino, dipentylamino, dihexylamino, N-methylethylamino or the like, in which preferable one is dimethylamino.

Suitable "lower alkylsilyl" may be mono, di, or tri(lower)alkylsilyl such as trimethylsilyl, dimethylsilyl, triethylsilyl or the like, in which preferable one is trimethylsilyl.

Suitable "lower alkylenedioxy" may be methylenedioxy, ethylenedioxy and the like, in which preferable one is methylenedioxy.

Suitable "heterocyclic group" in the definitions of general formulas [II-1]and [II-2] may be one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include

saturated or unsaturated, monocyclic or polycyclic heterocyclic group, and preferable heterocyclic group may be N-containing heterocyclic group such as

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;

saturated 3 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), [e.g. pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, homopiperazinyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, imidazopyridyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g. tetrazolo[1,5-b]pyridazinyl, etc.], quinoxalinyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;

saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, 1H-tetrahydropyranyl, tetrahydrofuranyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], oxazolinyl [e.g. 2-oxazolyinyl, etc.], etc.;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) [e.g. morpholinyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) [e.g. benzofurazanyl, benzoxazolyl, benzoxadiazolyl, etc.];

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, thiadiazolyl [e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) [e.g. thiazolidinyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 sulfur

atom(s) and 1 to 3 nitrogen atom(s) [e.g. benzothiazolyl, benzothiadiazolyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) [e.g. benzofuranyl, benzodioxolyl, chromanyl, etc.] and the like.

Said "heterocyclic group" may be substituted with lower alkyl as exemplified above, in which preferable one is thienyl, pyridyl, methylpyridyl, quinolyl, indolyl, quinoxalinyl, benzofuranyl or tetramethylchromanyl, and more preferable one is pyridyl.

Suitable "acyl" may be carboxy; esterified carboxy; carbamoyl substituted with lower alkyl, aryl, ar(lower)alky, arylsulfonyl, lower alkylsulfonyl or a heterocyclic group; substituted or unsubstituted arylsulfonyl;lower alkylsulfonyl; cyclo(lower)alkylcarbonyl;lower alkanoyl; substituted or unsubstituted aroyl; a heterocycliccarbonyl and the like.

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitorophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.], and the like, in which preferable one is unsubstituted lower alkoxycarbonyl and more preferable one is methoxycarbonyl or tert-butoxycarbonyl.

The carbamoyl substituted with lower alkyl may be methylcarbamoyl, ethycarbamoyl, propylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl and the like.

The carbamoyl substituted with aryl may be phenylcarbamoyl, naphthylcarbamoyl, lower alkyl-substituted phenylcarbamoyl [e.g. tolylcarbamoyl, xylylcarbamoyl, etc.] and the like.

The carbamoyl substituted with ar(lower)alkyl may be benzylcarbamoyl, phenethylcarbamoyl, phenylpropylcarbamoyl and the like, in which preferable one is benzylcarbamoyl.

The carbamoyl substituted with arylsulfonyl may be phenylsulfonylcarbamoyl, tolylsulfonylcarbamoyl and the like.

The carbamoyl substituted with lower alkylsulfonyl may be methylsulfonylcarbamoyl, ethylsulfonylcarbamoyl and the like.

The carbamoyl substituted with a heterocyclic group may be one substituted with a heterocyclic group as mentioned above for the definitions of general formulas [II-1]and [II-2].

The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like, in which preferable one is acetyl or pivaloyl.

The substituted or unsubstituted aroyl may be benzoyl, naphthoyl, toluoyl, di(tert-butyl)benzoyl, halo(lower)alkoxybenzoyl [e.g. trifluoromethoxybenzoyl, etc.] and the like, in which preferable one is benzoyl or trifluoromethoxybenzoyl.

The substituted or unsubstituted arylsulfonyl may be phenylsulfonyl, tolylsulfonyl, halophenylsulfonyl [e.g. fluorophenylsulfonyl, etc.] and the like, in which preferable one is fluorophenylsulfonyl.

The lower alkylsulfonyl may be methylsulfonyl, ethylsulfonyl and the like, in which preferable one is methylsulfonyl.

The cyclo(lower)alkylcarbonyl may be cyclo(C_3-C_6)alkylcarbonyl such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl or cyclohexylcarbonyl, in which preferable one is cyclopropylcarbonyl.

The heterocyclic moiety in the term "a heterocycliccarbonyl" may be one mentioned above as a heterocyclic group for the definitions of general formulas [II-1]and [II-2].

Suitable "N-protective group" may be common N-protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], lower alkoxycarbonyl [e.g. tert-butoxycarbonyl, tert-amyloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], 9-fluorenylmethoxycarbonyl, substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfeny, aralkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is lower alkoxycarbonyl and more preferable one is tert-butoxycarbonyl.

Suitable "cyclic hydrocarbon" may be a saturated or unsaturated cyclic hydrocarbon such as cyclopentane, cyclohexane, benzene, naphthalene, indan, indene or the like.

Suitable "substituted-lower alkyl" may be lower alkyl

substituted with halogen, aryl, acyl, lower alkoxy, aryloxy and the like, in which preferable one is benzyl.

Suitable "heterocyclic ring" may be one which is a heterocyclic group, as mentioned above for the definitions of general formulas [II-1]and [II-2], added by hydrogen.

Suitable lower alkylene condensed with a cyclic hydrocarbon may be lower alkylene condensed with benzene and the like, in which preferable one is ethylene condensed with benzene.

Suitable lower alkylene condensed with a heterocyclic ring may be lower alkylene condensed with pyridine and the like, in which preferable one is ethylene condensed with pyridine.

Preferred "acyl" for R^4 may be lower alkanoyl; lower alkoxycarbonyl; aroyl optionally substituted with halo(lower)alkoxy; arylsulfonyl optionally substituted with halogen; lower alkylsulfonyl; or cyclo(lower)alkylcarbonyl, in which more preferable one is acetyl, pivaloyl, methoxycarbonyl, tert-butoxycarbonyl, benzoyl, trifluoromethoxybenzoyl, fluorophenylsulfonyl, methylsulfonyl or cyclopropylcarbonyl.

Preferred "suitable substituent" as the substituent of lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group for R^7 may be halo(lower)alkyl, halo(lower)alkoxy, lower alkenyl, lower alkynyl, lower alkylamino, acylamino, acyl, lower alkylsilyl, lower alkoxy, aryl, lower alkylenedioxy, acyloxy, hydroxy, nitro, amino, cyano, halogen, aryloxy, lower alkylthio and the like.

Preferred "aryl which may be substituted with suitable substituent(s)" for R^7 may be aryl optionally substituted with halogen, in which more preferable one is fluorophenyl.

Preferred "arylamino which may be substituted with suitable substituent(s)" for R^7 may be arylamino optionally substituted with halogen, in which preferable one is phenylamino or fluorophenylamino.

Preferred "aryloxy which may be substituted with suitable substituent(s)" for R^7 may be aryloxy optionally substituted with halogen, in which preferable one is fluorophenoxy.

Preferred "lower alkylene" for J may be methylene.

Preferred "lower alkyl" for R^8 in J may be methyl.

Preferred "N-protective group" for R^8 in J may be tert-butoxycarbonyl.

Preferred "suitable substituent" as the substituent of lower alkylene for E may be oxo, lower alkyl, hydroxy(lower)alkyl or acyl, in which more preferable one is oxo, dioxo, methyl, dimethyl, hydroxymethyl, or benzylcarbamoyl.

Preferred "lower alkylene" for E may be methylene, ethylene or trimethylene, and more preferable one is ethylene.

Preferred "lower alkyl" for R^5 and R^6 may be methyl.

Preferred "lower alkylene which R^5 and R^6 are taken together to form" may be ethylene or trimethylene.

Preferred "a cyclic hydrocarbon with which lower alkylene is condensed" may be benzene.

Another more preferred compound [II-2] is one having lower alkanoyl, lower alkoxycarbonyl, aroyl, aroyl substituted with halo(lower)alkoxy, lower alkylsulfonyl, arylsulfonyl, arylsulfonyl substituted with halogen, or cyclo(lower)alkylcarbonyl for R^4, aryl or arylamino, each aryl of which may be substituted with halogen for R^7, N for X, a single bond for J, and -CO- for Q.

Another most preferred compound [II-2] is one selected from the group consisting of

1-acetyl-4-(4-flurophenylcarbamoyl)piperazine,

1-tert-butoxycarbonyl-4-(4-fluorophenylcarbamoyl)piperazine,

1-(4-fluorophenylcarbamoyl)-4-(4-trifluoromethoxybenzoyl)-piperazine and

1-methoxycarbonyl-4-(4-fluorophenylcarbamoyl)piperazine.

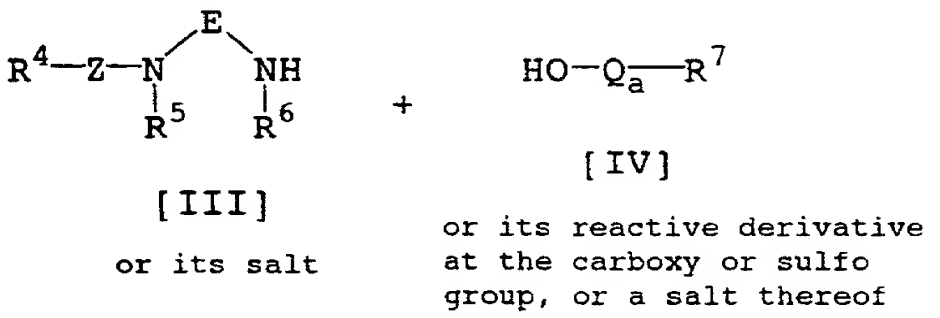
Suitable pharmaceutically acceptable salts of the compounds of general formulas [I], [II-1] and [II-2] are conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.], a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] and the like.

Compounds of the formula [I] and salts thereof can be prepared

according to the method disclosed in EP Publication No. 436734.

Compounds of the formula [II-1] including compounds [II-2] and salts thereof can be prepared by the processes as illustrated in the following reaction schemes.

Process 1



[III]

or its salt

+

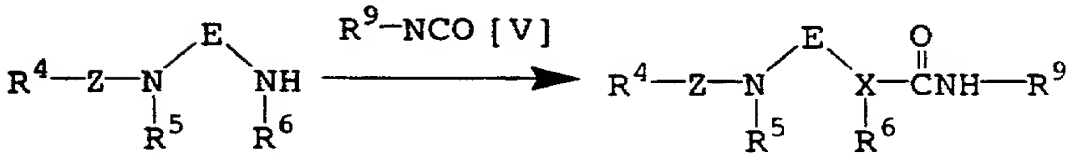
[IV]

or its reactive derivative at the carboxy or sulfo group, or a salt thereof

[II-1-a]

or its salt

Process 2



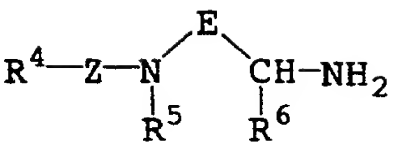
[III]

or its salt

[II-1-b]

or its salt

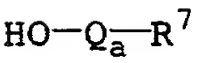
Process 3



[VI]

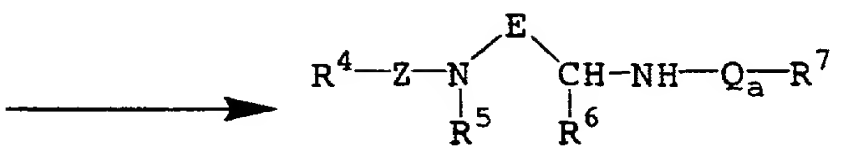
or its salt

+



[IV]

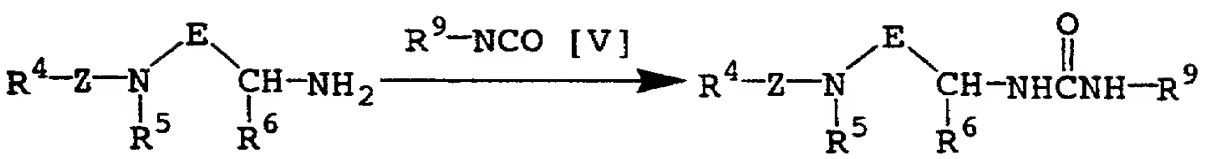
or its reactive derivative at the carboxy or sulfo group, or a salt thereof



[II-1-c]

or its salt

Process 4



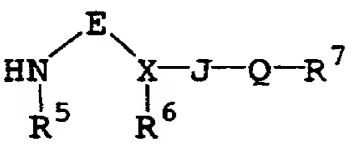
[VI]

or its salt

[II-1-d]

or its salt

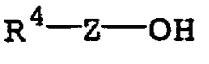
Process 5



[VII]

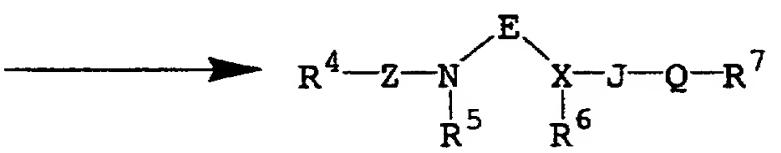
or its salt

+



[VIII]

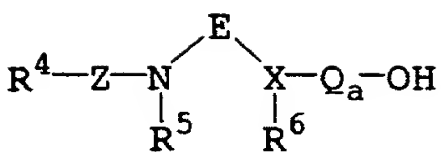
or its reactive derivative at the carboxy or sulfo group, or a salt thereof



[II-1]

or its salt

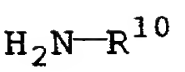
Process 6



[IX]

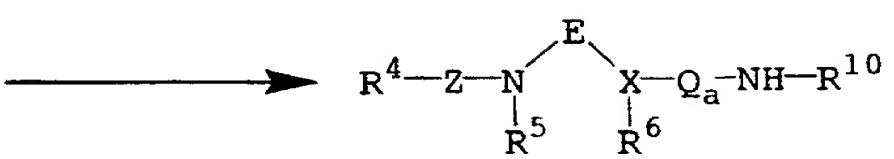
or its reactive derivative at the carboxy or sulfo group, or a salt thereof

+



[X]

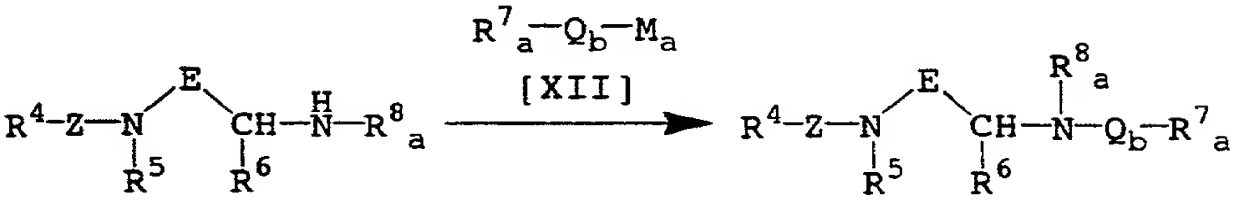
or its salt



[II-1-e]

or its salt

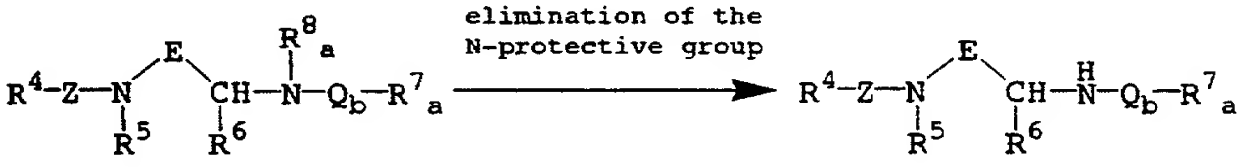
Process 7



[XI]
or its salt

[II-1-f]
or its salt

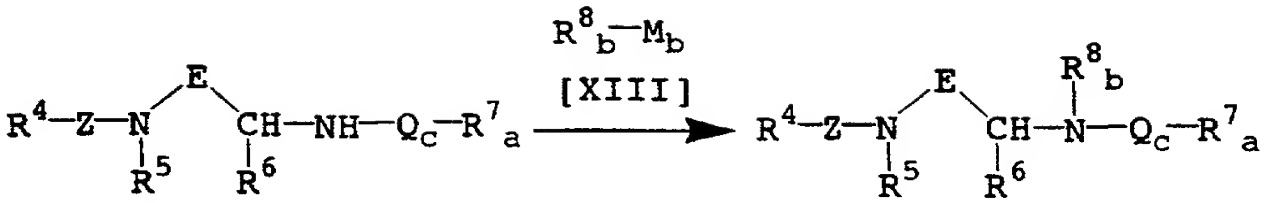
Process 8



[II-1-f]
or its salt

[II-1-g]
or its salt

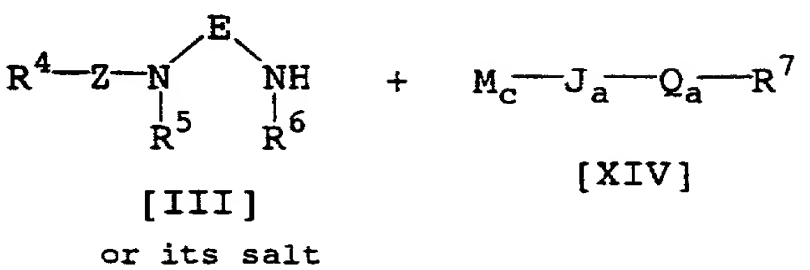
Process 9



[II-1-h]
or its salt

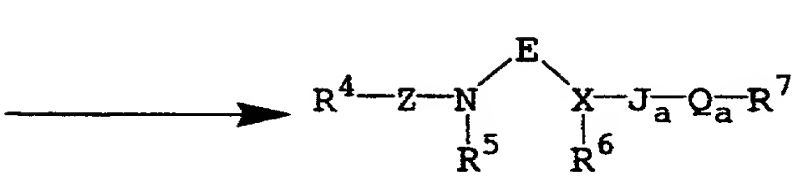
[II-1-i]
or its salt

Process 10



[III]
or its salt

[XIV]



[II-1-j]
or its salt

wherein R^4, R^5, R^6, R^7, Z, E, Q, X and J are each as defined above,

Q_a is -CO- or $-SO_2-$,

R^9 is aryl which may be substituted with suitable substituent(s), or pyridyl,

R^{10} is lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or a heterocyclic group, each of which may be substituted with suitable substituent(s),

R^8_a is an N-protective group,

R^7_a is lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or a heterocyclic group, each of which may be substituted with suitable substituent(s),

Q_b is $-CH_2-$, -CO-, or $-SO_2-$,

M_a is an acid residue,
Q_c is -CO-,
R^8_b is lower alkyl,
M_b is an acid residue,
M_c is an acid residue, and
J_a is lower alkylene.

Suitable "acid residue" may be halogen [e.g. floro, chloro, bromo, iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethansulfonyloxy, etc.], and the like, in which preferable one is halogen.

The processes for preparing the compounds [II-1] including compounds [II-2] are explained in detail in the following.

Process 1

The compound [II-1-a] or its salt can be prepared by reacting a compound [III] or its salt with a compound [IV] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

Suitable salts of the compounds [II-1-a] and [III] may be the same as those exemplified for the compound [II-1].

Suitable salts of the compound [IV] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [II-1].

Suitable reactive derivative at the carboxy or sulfo group of the compound [IV] may include an ester, an acid halide, an acid anhydride and the like. The suitable examples of the reactive derivatives may be an acid halide [e.g. acid chloride, acid bromide, etc.]; a symmetrical acid anhydride; a mixed acid anhydride with an acid such as aliphatic carboxylic acid [e.g. acetic acid, pivalic acid, etc.], substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.]; an ester such as substituted or unsubstituted lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl ester, trichloromethyl ester, etc.], substituted or unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, benzhydryl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, or the like. These reactive

derivatives can be optionally selected according to the kind of the compound [IV] to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene dichloride, tetrahydrofuran, acetonitrile, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvent may be used in a mixture with water.

The reaction is also preferably carried out in the presence of a conventional base such as triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaminopyridine, etc., or a mixture thereof.

When the compound [IV] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, thionyl chloride, oxalyl chloride, lower alkoxycarbonyl halide [e.g. ethyl chloroformate, isobutyl chloroformate, etc.], 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

The compound [II-1-b] or its salt can be prepared by reacting a compound [III] or its salt with a compound [V].

Suitable salts of the compound [II-1-b] and [III] may be the same as those exemplified for the compound [II-1].

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

The compound [II-1-c] or its salt can be prepared by reacting a compound [VI] or its salt with a compound [IV] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

Suitable salts of the compounds [II-1-c] and [VI] may be the same as those exemplified for the compound [II-1].

Suitable salts of the compound [VI] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 4

The compound [II-1-d] or its salt can be prepared by reacting a compound [VI] or its salt with a compound [V].

Suitable salts of the compound [II-1-d] and [VI] may be the same as those exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 2.

Process 5

The compound [II-1] or its salt can be prepared by reacting a compound [VII] or its salt with a compound [VIII] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

Suitable salt of the compound [VII] may be acid addition salt as exemplified for the compound [II-1].

Suitable salts of the compound [VIII] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 6

The compound [II-1-e] or its salt can be prepared by reacting a compound [IX] or its reactive derivative at the carboxy group or sulfo group, or a salt thereof with a compound [X] or its salt.

Suitable salts of the compounds [II-1-e], [IX] and its reactive derivative at the carboxy or sulfo group may be the same as those exemplified for the compound [II-1].

Suitable salt of the compound [X] may be acid addition salt as exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 7

The compound [II-1-f] can be prepared by reacting a compound [XI] or its salt with a compound [XII].

Suitable salts of the compounds [II-1-f] and [XI] may be the same as those exemplified for the compound [II-1].

The present reaction is preferably carried out in the presence of base such as an alkali metal [e.g. lithium, sodium, potassium, etc.], alkaline earth metal [e.g. calcium, etc.], alkali metal hydride [e.g. sodium hydride, etc.], alkaline earth metal hydride [e.g. calcium hydride, etc.], the hydroxide or carbonate or bicarbonate of an alkali metal or an alkaline earth metal [e.g. potassium bicarbonate, etc.] and the like.

This reaction is usually carried out in a solvent such as N,N-dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 8

The object compound [II-1-g] of its salt can be prepared by subjecting a compound [II-1-f] or its salt to elimination reaction of the N-protective group.

Suitable salts of the compounds [II-1-f] and [II-1-g] may be acid addition salts as exemplified for the compound [II-1].

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, alkylamine [e.g. methylamine,

trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using in trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, dioxane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullmann copper, etc.] and the like.

In case that the N-protective group is benzyl, the reduction is preferably carried out in the presence of a combination of palladium catalysts [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling the heating.

Process 9

The compound [II-1-i] or its salt can be prepared by reacting a compound [II-1-h] or its salt with a compound [XIII].

Suitable salts of the compounds [II-1-h] and [II-1-i] may be the same as those exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 7, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 7.

Process 10

The compound [II-1-j] or its salt can be prepared by reacting a compound [III] or its salt with a compound [XIV].

Suitable salts of the compounds [II-1-j] and [III] may be the same as those exemplified for the compound [II-1].

This reaction can be carried out in substantially the same manner as Process 7, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 7.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compounds [I], [II-1], [II-2] and the other compounds may include one or more stereoisomer(s) such as

optical isomer(s) or geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixture thereof are included within the scope of this invention.
Additionally, it is to be noted that any solvate [e.g. enclosure compound (e.g. hydrate, etc.)] of the compound [I], [II-1], [II-2] and pharmaceutically acceptable salts thereof is also included within the scope of this invention.

With regard to the brain somatostatin release promoting property, the brain somatostatin release promoting property is said to be expressed and the compound is said to have a brain somatostatin activation property, when the release amount of somatostatin by depolarization stimulation is increased due to a pretreatment of a hippocampal slice with a certain compound, as compared to when the pretreatment with the compound is void.

With regard to the property of increasing biosynthesis of somatostatin, the property of increasing biosynthesis of somatostatin in nerve cells is said to be expressed and the compound is said to have a brain somatostatin activation property, when a somatostatin content of the nerve cells is increased in the nerve cells due to a pretreatment with a certain compound, as compared to when the pretreatment with the compound is void.

With regard to the somatostatin receptor activation property, the somatostatin receptor activation property is said to be expressed and the compound is said to have a brain somatostatin activation property, when binding of somatostatin labeled with a radioisotope (e.g., ^{125}I and the like) to a somatostatin receptor in the nerve cells decreases due to a pretreatment with a certain compound, as compared to when the pretreatment with the compound is void.

With regard to the potentiation property of the expression of somatostatin property, the potentiation property of the expression of somatostatin property is said to be expressed and the compound is said to have a brain somatostatin activation property, when the activity of somatostatin degrading enzyme in the nerve cells is suppressed due to a pretreatment with a certain compound, as compared to when the pretreatment with the compound is void.

With regard to the potentiation property of the somatostatin signal transmission, the potentiation property of the somatostatin

signal transmission is said to be expressed and the compound is said to have a brain somatostatin activation property, when the amount of intracellular phosphorylated protein in the nerve cells changes due to a pretreatment with a certain compound, as compared to when the pretreatment with the compound is void.

With regard to the property of suppressing the negative feedback mechanism of brain somatostatin release, the property of suppressing the negative feedback mechanism of brain somatostatin release is said to be expressed and the compound is said to have a brain somatostatin release promoting property, when the suppressive action on the membrane potential dependent calcium current by somatostatin in the hippocampus pyramidal cells is released due to a pretreatment with a certain compound.

Agent for expression of long-term potentiation of synaptic transmission

The compound having a brain somatostatin activation property expresses the long-term potentiation of synaptic transmission.

Therefore, this compound is used as an agent for expression of long-term potentiation of synaptic transmission for mammals such as human, dog, cow, horse, rat, guinea pig and the like.

In the present invention, an agent for expression of long-term potentiation of synaptic transmission means a compound capable of inducing potentiation of general neurotransmission efficiency after high frequency and short time stimulation and sustaining the increased transmission efficiency for a long time.

The site where the long-term potentiation of synaptic transmission is expressed is subject to no limitation as long as it is a nerve system present in the hippocampus. Examples thereof include nerve systems present in brain, such as cerebral cortex, corpus amygdaloideum and the like, with preference given to the mossy fiber - CA3 pathway, perforant path-dentate gyrus pathway and Schaffer collaterals-CA1 pathway.

The agent for expression of long-term potentiation of synaptic transmission of the present invention is effective for the prophylaxis and/or treatment of cerebral diseases such as dementia (e.g., senile dementia, Alzheimer's dementia, dementia associated with various diseases such as cerebral vascular dementia, cerebral post-traumatic dementia, dementia due to brain tumor, dementia due to chronic subdural hematoma, dementia due to normal pressure hydrocephalus, post-meningitis dementia, Parkinson's disease type dementia, and the

like), amnesia, manic-depressive psychosis, schizophrenia, Parkinson's disease, psychosomatic disease, and the like, particularly for the prophylaxis and/or treatment of dementia and amnesia.

The long-term potentiation of synaptic transmission is evaluated according to the following criteria.

In a long-term potentiation phenomenon observed in the hippocampus of an animal, namely, guinea pig, which is observed according to the method conventionally known (Matsuoka et al., *Brain Research*, vol. 553, p. 188, 1991), when a pretreatment of hippocampus with a certain compound (bringing hippocampus into contact with the compound) leads to the augmentation of LTP, after tetanic stimulation, of potential generated from the CA3 field pyramidal cell caused by stimulation of mossy fiber to not less than 120%, preferably not less than 140%, more preferably not less than 160%, still more preferably not less than 180%, most preferably not less than 200%, when that without the pretreatment with the compound is 100%, the long-term potentiation of synaptic transmission is said to be expressed, and this compound can be said to be an agent for expression of long-term potentiation of synaptic transmission.

Alternatively, in a long-term potentiating phenomenon observed in the hippocampus of an animal, namely, guinea pig, which is observed according to the method conventionally known (Matsuoka et al., *Brain Research*, vol. 553, p. 188, 1991), when a long-term potentiation phenomenon is expressed in a sustained manner for not less than 10 minutes, preferably not less than 20 minutes, more preferably not less than 30 minutes, most preferably not less than 60 minutes due to a pretreatment with a certain compound, a long-term potentiation of synaptic transmission is said to be expressed and this compound can be said to be an agent for expression of long-term potentiation of synaptic transmission.

Note that variations in numerical values to the degree that those of ordinary skill in the art consider substantially the same statistically as the above-mentioned numerical values should be construed as corresponding to the above-mentioned numerical values.

As used herein, the pretreatment with a certain compound can be conducted by, for example, immersing the compound generally for 25 minutes in an outer solution containing hippocampus therein, and removing the compound by a method such as washing.

The test method for the evaluation of the above-mentioned long-term potentiation of synaptic transmission may be a method conventionally known or a method analogous thereto, with preference given to the following method.

Round slices are prepared from the hippocampus removed from an animal, for example, guinea pig. The slices are 500 μm in thickness. Each slice is placed in a container such as a perfusion chamber and the population spikes are extracellularly recorded in the following manner while perfusing with an artificial cerebrospinal fluid at 33 - 34℃ at a flow rate of 1.8 - 2.0 ml/min.

At this time, the test compound is added to the perfusate so that the concentration of the test compound in each container would be a serially diluted concentration, and the test compound is applied to the hippocampal slices from 21 minutes before the tetanic stimulation to 4 minutes thereafter.

The artificial cerebrospinal fluid to be used here is exemplified by those used in the screening method in the present invention to be mentioned later.

Mossy fiber is stimulated with a stimulation electrode at a voltage of not more than 10 V, frequency of 0.2 Hz, and the population spikes in the CA3 field pyramidal cell layer are recorded every 5 minutes. When the population spikes to be recorded are stabilized, tetanic stimulation is applied for the induction of LTP. The tetanic stimulation includes stimulation at the same voltage and a frequency of 33 Hz for 5 seconds. The height of from the negative peak to the next positive peak of the obtained population spikes after stimulation is measured and taken as an amplitude of population spikes. The degree of LTP can be expressed by a potential variation (%) showing an increase in the amplitude of population spikes after tetanic stimulation relative to the average of 4 measurements of the amplitudes of population spikes before tetanic stimulation. As the index of the property of a drug, the area in the graph of time lapse versus potential variation, between the graph from 12 minutes to 62 minutes after tetanic stimulation and the line where the potential variation is 0%, may be calculated and taken as the magnitude of LTP.

Each value of the potential variation and the magnitude of LTP which is calculated based on the potential variation as mentioned above is subjected to one-way analysis of variance and Dunnett's multiple

comparison test, and compared based on the above-mentioned evaluation criteria, whereby the long-term potentiation of synaptic transmission can be evaluated.

screening method

The screening method of the present invention comprises screening of the test compound to be screened (hereinafter to be abbreviated as a test compound) using the somatostatin releasing property as an index.

The screening method of the agent for expression of long-term potentiation of synaptic transmission of the present invention, particularly, an anti-dementia agent and an anti-amnesia agent, is a selection method of the test compound characteristically comprising bringing human or animal nerve cells into contact with a test compound, measuring an amount of somatostatin released from the nerve cells and a release time thereof, measuring an amount of somatostatin released from the nerve cells and a release time thereof in the absence of a contact with the test compound, and comparing the amounts and the times to measure the amount of somatostatin released from the nerve cells and the release time thereof caused by the contact with the test compound.

The above-mentioned nerve cells include, for example, hippocampus, preferably hippocampal slices, primary culture nerve cell, nerve cell strain, oocyte and the like.

The contact with the test compound can be conducted by, for example, immersing the test compound for 20 - 120 minutes in an outer solution in which the nerve cells are immersed and removing the test compound by washing and the like.

Preferred screening method is as follows.

Hippocampal slices are prepared from an animal (e.g., rat, guinea pig, mouse and the like) by a method conventionally known or a method analogous thereto. The slices are generally 100 - 600 μm, preferably 300 - 400 μm, in thickness. While the direction of slicing is not particularly limited, they are preferably transverse slices or longitudinal slices. For example, the slices are placed in a container such as a perfusion chamber, by generally 30 slices, more preferably 20 slices, and perfused with an artificial cerebrospinal fluid while incubating at generally 20 - 37℃, preferably 36 - 37℃. The perfusate is exchanged every 5 - 20 minutes, preferably 10 - 15 minutes. Fractions are obtained from each cycle, which step is repeated 10 to 20 times,

preferably 15 times. While repeatedly obtaining the fractions, the test compound is added to the perfusate to serially diluted concentrations that are within the range of preferably 10^{-10} - 10^{-5} M, more preferably 10^{-9} - 10^{-6} M, whereby fractions containing the test compound at respective concentrations are obtained. The test compound is immersed in perfusate for generally 20 - 120 minutes, preferably 80 minutes.

Generally 0 - 60 minutes, preferably 10 - 30 minutes, after the addition of the test compound, stimulation is preferably added. The stimulation is applied for generally 5 - 20 minutes, preferably 10 - 15 minutes. It is important that the stimulation be applied after the addition of the test compound, but the stimulation may be applied while the test compound is present in the perfusate or after the test compound is removed by washing with a perfusate.

The somatostatin in the perfusate of each fraction obtained as above is quantified according to a treatment method conventionally known (for example, perfusare is lyophilized and subjected to a radioimmunoassay). After the completion of the step for obtaining the fractions, the somatostatin remaining in hippocampal slices is extracted by a conventional method, which amount is similarly quantified.

The composition of the artificial cerebrospinal fluid to be used as the perfusate in the above-mentioned screening method can be modified as appropriate depending on the test conditions and test compound and the like to be used. Preferable composition includes the following. Artificial cerebrospinal fluid composition: NaCl, 124 mM; KCl, 5 mM; KH_2PO_4, 1.24 mM; $MgSO_4$, 1.3 mM; $CaCl_2$, 2.4 mM; $NaHCO_3$, 26 mM; D-glucose, 10 mM

This perfusate is used with saturation with a mixed gas of oxygen and carbon dioxide, such as a mixed gas of oxygen (95%) and carbon dioxide (5%), typically used for pharmacological experiments.

The above-mentioned screening method may be modified as necessary.

The amount of somatostatin quantified is compared with the amount when the contact with the test compound is void, based on the following criteria, whereby the somatostatin release promoting property of the test compound can be evaluated.

The screening method of the present invention is preferably

conducted under stimulation as mentioned above. Such stimulation is a model of a specific stimulation related to learning or tetanic stimulation. The stimulation is not particularly limited as long as the nerve cells present in the hippocampal slice are exited. Specific examples thereof include stimulation by potassium ion, electric stimulation, depolarization stimulation, stimulation with a drug and the like. When a mere addition of the test compound does not lead to the somatostatin release property and the test compound shows somatostatin release property only upon stimulation, it can be a confirmation that the nerve cells are free from influence of this test compound as long as no stimulation is involved, thus ensuring the safety of this compound.

The somatostatin release property is evaluated based on the following criteria.

In the screening method of the present invention, when the somatostatin release amount due to the contact with the test compound increases by not less than 10%, preferably not less than 20%, more preferably not less than 30%, still more preferably not less than 40%, most preferably not less than 50%, as compared to the release amount when the contact with the test compound is void (which is taken as 100%), the test compound is said to have a somatostatin release promoting property. It is preferable that the somatostatin release amount upon stimulation mentioned above be evaluated according to the above-mentioned criteria. It is appreciated that variations in numerical values to the degree that those of ordinary skill in the art consider substantially the same statistically as the above-mentioned numerical values should be construed as corresponding to the above-mentioned numerical values.

The test compound to be subject to the screening in the present invention is free of any particular limitation and may be selected from natural product, chemically synthesized compound, nucleic acid, peptide, antibody and the like obtained by genetic engineering and their libraries. The test compound is preferably a pure substance, but may be a mixture or racemic compound. The test compound may be also modified to label with radioisotope or may contain modification made during construction of library. The obtained test compound can be optimized by chemical synthetic method and the like.

By selecting the test compounds using the screening method of

the present invention, an agent for expression of long-term potentiation of synaptic transmission, particularly an anti-dementia agent, an anti-amnesia agent and the like can be screened.

The test compound selected by the screening method of the present invention and a compound obtained by optimizing this compound are all encompassed in the scope of the present invention.

The compound of the present invention having a brain somatostatin activation property can be used in the dosage form of a solid, semi-solid or liquid preparation in conjunction with organic or inorganic carrier or excipient, which is suitable for rectal administration, pulmonary (pernasal or buckle inhalation), nasal drop, eye drop, external (local), oral or parenteral (subcutaneous, intravenous or intramuscular) administration and the like, direct administration to diseased region, such as brain, spinal fluid, cerebroventricle and the like, or inhalation.

A compound having a brain somatostatin activation property can be admixed with pharmaceutically acceptable substantially non-toxic carrier or excipient conventionally used for dosage forms suitable for use, such as tablets, pellets, troches, capsules, suppositories, cream, ointment, aerosol, inhalable powder medicine, liquid, emulsion, suspension, and the like. Where necessary, auxiliary, stabilizer, tackifier, coloring agent and flavor can be used.

The agent for the expression of long-term potentiation of synaptic transmission, particularly an anti-dementia agent and an anti-amnesia agent, of the present invention can be produced by a method conventionally used in the pertinent field. Where necessary, a method routinely used in this technical field can be used for the production of these drugs for an improved bioavailability.

The agent for the expression of long-term potentiation of synaptic transmission, particularly an anti-dementia agent and an anti-amnesia agent, of the present invention is preferably administered intravenously (inclusive of addition into infusion), intramuscularly or orally when applying to humans or animals.

The agent for the expression of long-term potentiation of synaptic transmission, particularly an anti-dementia agent and an anti-amnesia agent, of the present invention is contained in a preparation in an amount sufficient to provide a desired prophylactic and/or treatment effect on the progression and conditions of diseases.

The amount and administration route of the compound having a brain somatostatin activation property are subject to variation depending on the kind of compound, age and conditions of the patients to be the subject of the prophylaxis and/or treatment. When compound 1 is used, for example, the daily dose is 0.1 - 10 mg/kg body weight by oral administration, which is given once to several times a day for the treatment and/or prophylaxis of the aforementioned diseases.

The present invention is explained in more detail in the following by way of Examples that do not limit the present invention.

Examples

Experimental Example 1: Effect of compound 1 on somatostatin release from rat hippocampal slice

(1) method

Rat hippocampal slices (thickness 350 μm, round slice) were prepared by a standard method. Twenty rat hippocampal slices were placed in a perfusion chamber, incubated at 37°C and perfused by a batch method while exchanging the incubation buffer every 10 minutes. The incubation buffer used had the composition as noted below. A mixed gas of oxygen (95%) and carbon dioxide (5%) was used to saturate the buffer. Composition of incubation buffer: NaCl, 124 mM; KCl, 5 mM; KH_2PO_4, 1.24 mM; $MgSO_4$, 1.3 mM; $CaCl_2$, 2.4 mM; $NaHCO_3$, 26 mM; D-glucose, 10 mM

Perfusion for 150 minutes gave fractions 1-15. To fraction 9 was applied a high K^+ (50 mM) stimulation. Compound 1 was added to fractions 7 - 15 to the concentration of 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, respectively. Nothing was added to control group. The respective fractions thus obtained were concentrated by lyophilization and somatostatin in the perfusate was quantified by radioimmunoassay (RIA). After the completion of the experiment, somatostatin remaining in the slices was extracted by a conventional method and quantified by radioimmunoassay. The somatostatin amount released by high K^+ (50 mM) stimulation was calculated and the amount of somatostatin released due to the property of compound 1 was measured.

Somatostatin release (%) by compound 1 at each concentration was calculated as in the following. The somatostatin amount of each fraction was expressed by the percentage (%) relative to the somatostatin residual amount at the time the fraction was obtained. The value of fraction 8 immediately before high K^+ (50 mM) stimulation was taken as the base and the values exceeding the base value were added with

regard to fraction 9 and the subsequent peak fractions exceeding the base value to give somatostatin release (%). The number of the test samples measured was 10 or 11. Each value (%) was expressed by mean ±S.E.M. The property of compound 1 was subjected to Dunnett's multiple comparison test relative to control group.

(2) Result

The results are shown in Fig. 1. The compound 1 promoted somatostatin release when stimulated at high K^+ (50 mM), and the property was significant at 10^{-7} M and 10^{-6} M. The concentration dependency was similar to the long-term potentiation in Experimental Example 2 to be mentioned later. By the use of the screening method of the present invention, compound 1 was shown to have a somatostatin release promoting property on hippocampus.

Experimental Example 2: Effect of compound 1 on LTP in mossy fiber - CA3 field pyramidal cell of hippocampal slice

(1) method

Slices (thickness 500 μm, round slice) were prepared from hippocampus removed from male Hartley guinea pigs (body weight 220 - 350 g) and population spikes were extracellularly recorded. The hippocampal slices were perfused with an artificial cerebrospinal fluid (33-34℃, composition: NaCl, 124 mM; KCl, 5 mM; KH_2PO_4, 1.24 mM; $MgSO_4$, 1.3 mM; $CaCl_2$, 2.4 mM; $NaHCO_3$, 26 mM; D-glucose, 10 mM) saturated with a mixed gas of oxygen (95%) and carbon dioxide (5%) at flow rate of 1.8 - 2.0 ml/min. Mossy fiber was stimulated with a stimulating electrode at a voltage of not more than 10 V, frequency of 0.2 Hz and the population spikes in the CA3 field pyramidal cell layer was recorded every 5 minutes. When the population spikes to be recorded were stabilized, tetanic stimulation for induction of LTP was applied. The tetanic stimulation includes stimulation at the same voltage of not more than 10 V, as when the stimulation was applied at a frequency of 0.2 Hz, but upon increase of the frequency to 33 Hz for 5 seconds. The height of from negative peak to the next positive peak of the obtained population spikes after stimulation was measured and taken as an amplitude (population spike amplitude;PSA). The degree of LTP was expressed by a potential variation (%) by the increase in the amplitude of population spikes after tetanic stimulation relative to the average of 4 measurements of the amplitudes of population spikes obtained before tetanic stimulation. Each value was expressed by mean±S.E.M (the

number of slices tested was 3 to 8). As the index of the property of a drug, the area (%·min) between the graph from 12 minutes to 62 minutes after tetanic stimulation and the line where the potential variation is 0%, in the time lapse graph of potential variation, was calculated and taken as the magnitude of LTP. Compound 1 was dissolved in and diluted with distilled water and added to perfusate to the concentration of 10^{-9}M, 10^{-8}M, 10^{-7}M and 10^{-6}M, respectively, and applied to a hippocampal slice for 25 minutes from 2 minutes before the tetanic stimulation to 4 minutes thereafter. Nothing was added to perfusate for control group.

The property of compound 1 relative to the magnitude of LTP was tested by one-way analysis of variance and Dunnett's multiple comparison test.

(2) Results

From the potential variation with the lapse of time, compound 1 was found to have shown no significant influence of the response of base before tetanic stimulation. As is can be seen from Fig. 2 showing the magnitude of LTP, compound 1 increased potential variation after tetanic stimulation at 10^{-7} M and 10^{-6} M, wherein its action was maximal at 10^{-7}M. From the foregoing, it was shown that compound 1 had a promoting property specific to the mechanism necessary for the occurrence of phenomenon of long-term potentiation of synaptic transmission after tetanic stimulation.

The hippocampal slice obtained from the guinea pig treated with cysteamine (200 mg/kg) did not show LTP enhancing property by compound 1 at 10^{-7} M. This reveals that hippocampus endogeneous somatostatin activation property is involved in the LTP enhancing property by compound 1.

Experimental Example 3: Effect of compound 1 on voltage-dependent Ca^{2+} current of rat hippocampus pyramidal cell

(1) method

Hippocampal slices were prepared from the brains of 5- to 14-day-old male Wistar rats and the nerve cells were quickly isolated by trypsin enzyme treatment method. According to the whole cell patch-clamp method, the membrane potential of hippocampus pyramidal cell was fixed at -80 mV and the membrane potential-dependent potassium current (Ica) was measured in Cs^{+} electrode inner solution and Ba^{2+} bath outer solution. The resistance of the electrode was 2 - 4 MΩ.

Compound 1 was added to bath outer solution concentrations of 0.01 μM, 0.1 μM and 1.0 μM, respectively, and perfused with the bath outer solution. Nothing was added to the bath outer solution for the control group. The maximal value of the current (peak amplitude) was measured, and calculated as the variation (%) relative to the value before addition of compound 1. Each value (%) was expressed by mean±S.E.M. The number of measurements was 7. The property of compound 1 was evaluated by Dunnett's multiple comparison test relative to the control group.

(2) Result

The results are shown in Fig. 3. Compound 1 significantly promoted membrane potential-dependent calcium current at concentrations of 0.01 μM, 0.1 μM and 1.0 μM as compared to the control group, and showed bell-shape dose dependency. Therefore, compound 1 was shown to have a promoting action on the voltage-dependent calcium channel of hippocampus pyramidal cells.

Experimental Example 4: Effect of somatostatin and compound 1 on voltage-dependent Ca^{2+} current of rat hippocampus pyramidal cell

(1) method

In the same manner as in Experimental Example 3 except that compound 1 and somatostatin were added in such a manner that the concentration of somatostatin in the bath outer solution was 10^{-7} M when somatostatin alone was added, and the concentration of compound 1 in the bath outer solution was 10^{-7} M and the concentration of somatostatin in the bath outer solution was 10^{-7} M when both compound 1 and somatostatin were added, the experiment was conducted. Nothing was added to the control group. The maximal value of each current was measured, and calculated as the variation (%) to that prior to addition. Each value (%) was expressed by mean±S.E.M. The number of measurements of the group added with somatostatin was 11 and that of the group added with both compound 1 and somatostatin was 7. The both groups were subjected to Dunnett's multiple comparison test.

(2) Result

The results are shown in Fig. 4. While somatostatin evidently suppressed membrane potential-dependent calcium current, suppressive property of somatostatin was completely released in the presence of compound 1. Hence, compound 1 was shown to release the suppressive property of somatostatin on the voltage-dependent calcium channel of hippocampus pyramidal cell and has a promoting property. From the

results of Experimental Example 3 and this Experimental Example, compound 1 was shown to suppress the negative feedback mechanism of brain somatostatin release.

The compounds [II-1] including compounds [II-2] used in the present invention and preparation methods thereof are explained in detail by way of the following Reference preparations and Reference examples. It is needless to say that those Reference preparations and Reference examples do not limit the present invention.

Reference preparation 1

To a solution of 1-benzyl-4-aminopiperidine (50 g) in water (360 ml) was added a solution of di-tert-butyl dicarbonate (61 g) in acetone (360 ml) dropwise under cooling on an ice-water bath. After stirring for 2.5 hours, a precipitate was collected on a filter, washed with water, and dried. The crude product was poured into a mixture of diisopropyl ether (200 ml) and n-hexane (200 ml) and the mixture was stirred. After filtration, O-tert-butyl N-(1-benzylpiperidin-4-yl)-carbamate (66.9 g) was obtained.

NMR (DMSO-d_6, δ): 1.2-1.5 (2H, m), 1.37 (9H, s), 1.66 (2H, br d, J=9.9Hz), 1.91 (2H, br t J=10.7Hz), 2.73 (2H, distorted d, J=11.8Hz), 3.2 (1H, m), 3.41 (2H, s), 6.75 (1H, d, J=7.8Hz), 7.1-7.4 (5H, m)

MASS (APCI)(m/z): 291

Reference preparation 2

To a mixture of O-tert-butyl N-(1-benzylpiperidin-4-yl)-carbamate (45 g) and 10% palladium on carbon (50% wet, 9 g) in methanol (1 l) was bubbled hydrogen gas under stirring at ambient temperature. The catalyst was removed by glass filter and the solvent was removed under reduced pressure. After rinse with diisopropyl ether, O-tert-butyl N-(piperidin-4-yl)carbamate (28.35 g) was obtained. The washed solvent was removed under reduced pressure, and the residue was rinsed with diisopropyl ether. The second fraction of O-tert-butyl N-(piperidin-4-yl)carbamate (344 mg) was obtained.

NMR (DMSO-d_6, δ): 1.18 (2H, ddd, J=3.8, 11.8, 11.8Hz), 1.37 (9H, s), 1.62 (2H, distorted d, J=10.8Hz), 1.85(1H, m), 2.38 (2H, dt, J=2.2, 12.0Hz), 2.86 (2H, distorted d, J=12.3Hz), 3.2 (1H, m), 6.72 (1H, br d)

MASS (APCI)(m/z): 201

Reference preparation 3

To a suspension of O-tert-butyl N-(piperidin-4-yl)carbamate (4.0 g) in dichloromethane (40 ml) were added pyridine (1.94 ml), dichloromethane (40 ml), acetic anhydride (20.8 ml) and then N,N-dimethylaminopyridine (0.1 g) at ambient temperature. After stirring for 3 hours, the mixture was washed with 0.1N hydrochloric acid, water, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After rinse with diisopropyl ether, O-tert-butyl N-(1-acetylpiperidin-4-yl)carbamate (4.01 g) was obtained.

NMR (DMSO-d_6, δ): 1.23 (2H, m), 1.38 (9H, s), 1.70 (2H, distorted t, J=11.4Hz), 1.97 (3H, s), 2.64 (1H, br t, J=11.1Hz), 3.04 (1H, dt, J=2.8, 11.5Hz), 3.42 (1H, m), 3.72 (1H, br d, J=15.0Hz), 4.19 (1H, br d, J=13.1Hz), 6.86 (1H, d, J=7.5Hz)

MASS (APCI)(m/z): 243

Reference preparation 4

To a solution of O-tert-butyl N-(1-acetylpiperidin-4-yl)-carbamate (2.42 g) in dichloromethane (24 ml) was added 4N hydrogen chloride in dioxane (24 ml). The solvents were removed under reduced pressure. After rinse with diisopropyl ether, 1-acetyl-4-amino-piperidine hydrochloride (2.02 g) was obtained.

NMR (DMSO-d_6, δ): 1.41 (2H, m), 1.93 (2H, distorted t), 2.00 (3H, s), 2.60 (1H, br t, J=10.4Hz), 3.06 (1H, br t, J=11.3Hz), 3.12 (1H, m), 3.84 (1H, br d, J=14.0Hz), 4.34 (1H, br d, J=13.0Hz), 8.32 (3H, br s)

MASS (APCI)(m/z): 143

Reference preparation 5

To a solution of phenyl chloroformate (5.64 g) in dichloromethane (70 ml) was added a solution of 4-aminopyridine (2.84 g) and triethylamine (5.02 ml) in dichloromethane (100 ml) dropwise under cooling on an ice-water bath. After stirring for 1 hour, the solvents were removed under reduced pressure. A residue was diluted with dichloromethane (200 ml) and water (200 ml). An organic phase was separated and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. The reaction mixture was diluted with diisopropyl ether and the precipitates were filtered. After rinse with diethyl ether, O-phenyl N-(4-pyridyl)carbamate (5.07 g) was obtained.

NMR ($CDCl_3$, δ): 7.17 (2H, m), 7.27 (1H, m), 7.3-7.5 (4H, m), 8.50 (2H, dd, J=1.4, 5.0Hz), 8.06 (1H, s)

MASS (APCI)(m/z): 215

Reference preparation 6

A solution of sulfuryl chloride (3.55 ml) in chloroform (45 ml) was added a solution of 1-acetylpiperazine (5.66 mg) and triethylamine (6.16 ml) in chloroform (15 ml) dropwise under cooling on an ice-water bath. After stirring for 6 hours, a precipitate was collected by filtration. After drying over sodium hydroxide, 1-acetylpiperazine-4-sulfonyl chloride (2.43 g) was obtained.

NMR ($CDCl_3$, δ): 2.15 (3H, s), 3.35 (4H, m), 3.69 (2H, t, J=5.1Hz), 3.83 (2H, br s)

MASS (APCI)(m/z): 227

Reference preparation 7

To a solution of 1-benzyl-4-aminopiperidine (1.13 g) in dichloromethane (10 ml) were added a solution of 4-fluorobenzoyl chloride (0.99 g) in dichloromethane (1 ml) and diisopropylethylamine (1.09 ml) under cooling on an ice-water bath. The mixture was warmed to ambient temperature slowly under stirring. The mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, dichloromethane:methanol = 15:1). After rinse with diisopropyl ether - n-hexane (1:1), N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (1.31 g) was obtained.

NMR (DMSO-d_6, δ): 1.4-1.7 (2H, m), 1.7-1.9 (2H, m), 2.01 (2H, br t, J=10.7Hz), 2.81 (2H, br d, J=11.6Hz), 3.46 (2H, s), 3.73 (1H, m), 7.2-7.4 (7H, m), 7.90 (2H, dd, J=5.6, 8.9Hz), 8.26 (1H, br d, J=7.7Hz)

MASS (APCI)(m/z): 313

Reference preparation 8

The following compound was obtained by using 4-amino-1-benzylpiperidine as a starting compound according to a similar manner to that of Reference example 2.

N-(1-Benzylpiperidin-4-yl)-N'-(4-fluorophenyl)urea

NMR (DMSO-d_6, δ): 1.25-1.5 (2H, m), 1.7-1.9 (2H, m), 2.0-2.2 (2H, m), 2.65-2.8 (2H, m), 3.4-3.6 (3H, m), 6.07 (1H, d, J=7.6Hz),

7.05 (2H, t, J=9Hz), 7.2-7.45 (2H, m), 8.35 (1H, s)

MASS (APCI)(m/z): 328

Reference preparation 9

To a solution of N-(1-benzylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (3.0 g) in a mixture of methanol (15 ml) and tetrahydrofuran (15 ml) was added palladium on carbon (10% w/w, 50% wet, 0.6 g), and the mixture was hydrogenated under atmospheric pressure of hydrogen for 8 hours. The catalyst was filtered off, and the solvents were evaporated under reduced pressure to give a residue, which was triturated with diisopropyl ether to give N-(piperidin-4-yl)-N'-(4-fluorophenyl)urea (1.97 g).

NMR (DMSO-d_6, δ): 1.1-1.4 (2H, m), 1.65-1.85 (2H, m), 2.3-2.65 (2H, m), 2.8-3.0 (2H, m), 3.3-3.7 (1H, m), 6.08 (1H, d, J=8Hz), 7.04 (2H, t, J=9Hz), 7.25-7.5 (2H, m), 8.33 (1H, s)

MASS (APCI)(m/z): 238

Reference preparation 10

A mixture of N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (937 mg) and 10% palladium on carbon (50% wet, 0.2 g) in methanol (20 ml) was stirred under hydrogen atmosphere for 7.5 hours at ambient temperature. The catalyst was removed by glass filter and the solvent was removed under reduced pressure. After rinse with diisopropyl ether, N-(piperidin-4-yl)-4-fluorobenzamide (653 mg) was obtained.

NMR (DMSO-d_6, δ): 1.40 (2H, ddd, J=4.0, 11.9, 23.8Hz), 1.72 (2H, br d, J=9.5Hz), 2.3-2.7 (2H, m), 2.8-3.2 (2H, m), 3.80 (1H, m), 7.27 (2H, t, J=8.9Hz), 7.92 (2H, dd, J=5.6, 8.9Hz), 8.26 (1H, d, J=7.7Hz)

MASS (APCI)(m/z): 223

Reference example 1

To a solution of O-phenyl N-(4-pyridyl)carbamate (446 mg) in 1,2-dichloroethane (5 ml) was added a suspension of 1-acetylpiperazine (1.12 g) in 1,2-dichloroethane (20 ml) at ambient temperature. The mixture was heated at 60℃ with stirring for 9 hours. The mixture was cooled to ambient temperature, and diluted with dichloromethane and water. The aqueous phase was separated and adjusted to pH 11.5 with sodium hydroxide solution. Excess sodium chloride was added to the aqueous solution. The mixture was extracted with a mixture of dichloromethane and methanol (about 10:1) and the organic phase was washed with brine. After drying with magnesium sulfate, the solvents

were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, dichloromethane:methanol:aqueous ammonia = 10:1:0.1). After rinse with diisopropyl ether, 1-acetyl-4-(4-pyridylaminocarbonyl)piperazine (398 mg) was obtained.

NMR (DMSO-d_6, δ): 2.03 (3H, s), 3.3-3.6 (8H, m), 7.47 (2H, dd, J=1.5, 4.8Hz), 8.31 (2H, dd, J=1.5, 4.8Hz), 9.01 (1H, s)

MASS (APCI)(m/z): 271

Reference example 2

To a stirred solution of 1-acetylpiperazine (0.648 g) in tetrahydrofuran (10 ml) was added 4-fluorophenyl isocyanate (0.574 g) at ambient temperature. After stirring at ambient temperature for 1 hour, the solvent was removed by evaporation under reduced pressure, and the residue was triturated with diisopropyl ether to give 1-acetyl-4-(4-flurophenylcarbamoyl)piperazine (1.25 g).

NMR (DMSO-d_6, δ): 2.03 (3H, s), 3.3-3.6 (8H, m), 7.07 (2H, t, J=9Hz), 7.46 (2H, dd, J=5, 9Hz), 8.61 (1H, s)

MASS (APCI)(m/z): 266

Reference example 3

The following compound was obtained by using 1-tert-butoxycarbonylpiperazine as a starting compound according to a similar manner to that of Reference example 2.

1-tert-Butoxycarbonyl-4-(4-flurophenylcarbamoyl)piperazine

NMR (DMSO-d_6, δ): 1.42 (9H, s), 3.25-3.5 (8H, m), 7.07 (2H, t, J=9Hz), 7.45 (2H, dd, J=5, 9Hz), 8.60 (1H, s)

MASS (LD)(m/z): 346.2

Reference example 4

To a solution of pyridine-4-carboxylic acid (1.0 g) and triethylamine (1.2 ml) in toluene (20 ml) was added diphenylphosphoryl azide (1.75 ml) at ambient temperature. The resulting mixture was heated to reflux for 30 minutes and cooled to 0°C. To the mixture was added 1-tert-butoxycarbonylpiperazine (1.51 g), and the mixture was allowed to heat to 90°C for 1 hour. After cooling to ambient temperature, the reaction mixture was taken up into ethyl acetate, washed in turn with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was chromatographed on silica gel (150 ml) eluting with 0-7% methanol in dichloromethane. Trituration with a mixture of diisopropyl ether and ethanol gave 1-tert-butoxycarbonyl-4-(pyridin-4-ylcarbamoyl)piperazine (0.66 g).

NMR (DMSO-d_6, δ): 1.42 (9H, s), 3.25-3.5 (8H, m), 7.46 (2H, d, J=1.5, 5Hz), 8.30 (2H, d, J=1.5, 5Hz), 9.00 (1H, s)

MASS (LD)(m/z): 307.2

Reference example 5

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (0.4 g) in dichloromethane (5 ml) were added in turn pyridine (0.54 ml) and 4-fluorophenyl chloroformate (0.29 ml) at 0℃. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 1-acetyl-4-(4-flurophenoxycarbonyl-amino)piperidine (347 mg).

NMR (DMSO-d_6, δ): 1.15-1.55 (2H, m), 1.7-1.95 (2H, m), 2.00 (3H, s), 2.65-2.85 (1H, m), 3.0-3.25 (1H, m), 3.5-3.7 (1H, m), 3.7-3.9 (1H, m), 4.15-4.3 (1H, m), 7.05-7.3 (4H, m), 7.86 (1H, d, J=8Hz)

MASS (APCI)(m/z): 281

Reference example 6

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (715 mg) in dichloromethane (7 ml) were added diisopropylethylamine (1.83 ml) and a solution of 4-fluorobenzoyl chloride (0.83 mg) in dichloromethane (2 ml) at ambient temperature. After stirring for 6.5 hours, the reaction mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 50:1 to 10:1). After rinse with diisopropyl ether, N-(1-acetylpiperidin-4-yl)-4-fluoro-benzamide (738 mg) was obtained.

NMR (DMSO-d_6, δ): 1.40 (2H, m), 1.81 (2H, distorted t, J=12.4Hz), 2.01 (3H, s), 2.68 (1H, br t, J=11.4Hz), 3.13 (1H, br t, J=11.6Hz), 3.83 (1H, br t, J=13.9Hz), 4.01 (1H, m), 4.33 (1H, br d, J=13.7Hz), 7.29 (2H, t, J=8.9Hz), 7.92 (2H, dd, J=5.5, 8.8Hz), 8.31 (1H, d, J=7.7Hz)

MASS (APCI)(m/z): 265

Reference example 7

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (536

mg) in dichloromethane (5 ml) were added isonicotinoyl chloride hydrochloride (534 mg) and diisopropylethylamine (1.05 ml) at ambient temperature. After stirring for 8 hours, the reaction mixture was poured into water and diluted with dichloromethane. The mixture was adjusted to pH 8.5 with 1N sodium hydroxide solution. Sodium chloride was added to the mixture and an organic phase was separated. The aqueous phase was extracted with dichloromethane and a combined organic phase was dried over magnesium sulfate. The solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 10:1). After crystallization from diisopropyl ether:n-hexane, N-(1-acetylpiperidin-4-yl)-N-isonicotinamide (477 mg) was obtained.

NMR (DMSO-d_6, δ): 1.4 (2H, m), 1.83 (2H, distorted t, J=11Hz), 2.01 (3H, s), 2.69 (1H, br t, J=11Hz), 3.14 (1H, br t, J=12Hz), 3.83 (1H, br d, J=14.1Hz), 4.03 (1H, m), 4.33 (1H, br d, J=13.1Hz), 7.75 (2H, dd, J=1.7, 4.4Hz), 8.62 (1H, d, J=7.5Hz), 8.72 (2H, dd, J=1.6, 4.4Hz)

MASS (APCI)(m/z): 248

Reference example 8

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (715 mg) in dichloromethane (7 ml) were added diisopropylethylamine (1.83 ml) and a solution of 4-fluorobenzenesulfonyl chloride (0.83 mg) in dichloromethane (2 ml) at amibient temperature. After stirring for 6.5 hours, the reaction mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 50:1 to 20:1). After rinse with diisopropyl ether, N-(1-acetylpiperidin-4-yl)-4-fluoro-benzenesulfonamide (859 mg) was obtained.

NMR (DMSO-d_6, δ): 1.21 (2H, m), 1.54 (2H, m), 1.94 (3H, s), 2.66 (1H, br t, J=10.8Hz), 3.02 (1H, dt, J=2.9, 12.0Hz), 3.22 (1H, m), 3.64 (1H, br d, J=14.0Hz), 4.05 (1H, br d, J=13.2Hz), 7.44 (2H, t, J=8.9Hz), 7.8-8.0 (3H, m)

MASS (APCI)(m/z): 301

Reference example 9

To a solution of O-phenyl N-(4-pyridyl)carbamate (0.81 g) in chloroform (10 ml) were added 1-acetyl-4-aminopiperidine hydrochloride

(0.68 g) and triethylamine (1.06 ml) at ambient temperature. After stirring for 1 day, the mixture changed to a solution. The solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, dichloromethane:methanol = 10:1 to 5:1, and silica gel 50 ml, dichloromethane:methanol:aqueous ammonia =10:1:0.1). The solvents of desired fractons were removed under reduced pressure. A residue was dissolved with methanol (5 ml) and dichloromethane (5 ml), and 4N hydrogen chloride in dioxane (1.5 ml) was added to the solution. The solvents were removed under reduced pressure, and the residue was evaporated azeotropically with methanol. After crystallization from diisopropyl ether and n-hexane, N-(1-acetylpiperidin-4-yl)-N'-(4-pyridyl)urea (343 mg) was obtained.

NMR (DMSO-d_6, δ): 1.1-1.6 (2H, m), 1.77 (2H, m), 2.01 (3H, s), 2.94 (1H, br t, J=10.4Hz), 3.22 (1H, br t, J=10.1Hz), 3.76 (2H, m), 4.05 (1H, d, J=13.6Hz), 7.60 (1H, d, J=7.8Hz), 7.83 (2H, d, J=6.8Hz), 8.52 (2H, d, J=7.1Hz), 11.21 (1H, s), 14.66 (1H, br s)

MASS (APCI)(m/z): 263

Reference example 10

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (536 mg) in dichloromethane (5 ml) were added 4-florophenyl isocyanate (375 μl) and diisopropylethylamine (575 μl) at ambient temperature. After stirring for 3 hours, the reaction mixture was diluted with dichloromethane. An organic phase was separated and an aqueous phase was extracted with dichloromethane. A combined organic phase was dried over magnesium sulfate and the solvents were removed under reduced pressure. After crystallization from diisopropyl ether and n-hexane, N-(1-acetylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (448 mg) was obtained.

NMR (DMSO-d_6, δ): 1.1-1.5 (2H, m), 1.80 (2H, distorted t, J=10Hz), 2.00 (3H, s), 2.77 (1H, br d, J=10.8Hz), 3.14 (1H, br d, J=11.1Hz), 3.5-3.9 (2H, m), 4.16 (1H, br d, J=13.2Hz), 6.15 (1H, d, J=7.6Hz), 7.05 (2H, t, J=8.9Hz), 7.40 (2H, dd, J=5.0, 9.2Hz), 8.37 (1H, s)

MASS (APCI)(m/z): 280

Reference example 11

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.25 g) in dichloromethane (5 ml) were added in turn pyridine (0.14 ml) and methyl chloroformate (87 μl) at 0°C. The mixture was allowed to warm

to ambient temperature and stirred for 1 hour. To the mixture was added N,N-dimethylaminopyridine (0.13 g) and allowed to stir for another 1 hour. The reaction mixture was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-(4-fluorobenzoylamino)-1-methoxycarbonylpiperidine (0.265 g).

NMR (DMSO-d_6, δ): 1.3-1.6 (2H, m), 1.75-1.9 (2H, m), 2.8-3.05 (2H, m), 3.60 (3H, s), 3.85-4.1 (2H, m), 7.29 (2H, t, J=9Hz), 7.90 (2H, dd, J=6, 9Hz), 8.30 (1H, d, J=8Hz)

MASS (APCI)(m/z): 281

Reference example 12

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.25 g) in pyridine (5 ml) were added in turn 4-fluorobenzenesulfonyl chloride (0.219 g) and catalytic amount of N,N-dimethylaminopyridine at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of water and dichloromethane. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-(4-fluorobenzoylamino)-1-(4-fluorophenylsulfonyl)piperidine (0.38 g).

NMR (DMSO-d_6, δ): 1.45-1.7 (2H, m), 1.8-1.95 (2H, m), 2.35-2.55 (2H, m), 3.5-3.85 (3H, m), 7.28 (2H, t, J=9Hz), 7.50 (2H, t, J=9Hz), 7.75-7.95 (4H, m), 8.31 (1H, d, J=8Hz)

MASS (APCI)(m/z): 381

Reference example 13

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.15 g) in dichloromethane (5 ml) were added in turn pyridine (82 μl) and 4-trifluoromethoxybenzyol chloride (106 μl) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 4 hours, which was taken up into a mixture of water and dichloromethane. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave 4-(4-fluorobenzoylamino)-1-(4-trifluoromethoxybenzoyl)piperidine

(205 mg).

NMR (DMSO-d_6, δ): 1.3-1.7 (2H, m), 1.7-2.0 (2H, m), 2.7-3.4 (2H, m), 3.4-3.8 (1H, m), 3.9-4.2 (1H, m), 4.2-4.6 (1H, m), 7.30 (2H, t, J=9Hz), 7.35-7.6 (4H, m), 7.91 (2H, dd, J=6, 9Hz), 8.35 (1H, d, J=8Hz)

MASS (LD)(m/z): 433.2

Reference example 14

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.15 g) in dichloromethane (5 ml) were added in turn pyridine (0.14 ml) and methanesulfonyl chloride (96 μl) at 0℃. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. To the mixture was added N,N-dimethylaminopyridine (0.13 g) and allowed to stir for another 1 hour. The reaction mixture was taken up into a mixture of water and dichloromethane. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-(4-fluorobenzoylamino)-1-methylsulfonylpiperidine (0.30 g).

NMR (DMSO-d_6, δ): 1.45-1.7 (2H, m), 1.8-2.05 (2H, m), 2.7-2.95 (2H, m), 2.88 (3H, s), 3.5-3.65 (2H, m), 3.8-4.05 (1H, m), 7.30 (2H, t, J=9Hz), 7.91 (2H, dd, J=6, 9Hz), 8.36 (1H, d, J=8Hz)

MASS (APCI)(m/z): 301

Reference example 15

To a solution of N-(piperidin-4-yl)-N'-(4-fluorophenyl)-urea (0.3 g) in tetrahydrofuran (4 ml) were added in turn pyridine (0.28 ml), methyl chloroformate (98 μl) and catalytic amount of N,N-dimethylaminopyridine at 0℃. The mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give N-(1-methoxycarbonylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (0.312 g).

NMR (DMSO-d_6, δ): 1.1-1.4 (2H, m), 1.7-1.9 (2H, m), 2.8-3.1 (2H, m), 3.5-3.75 (1H, m), 3.59 (3H, s), 3.75-3.95 (2H, m), 6.15 (1H, d, J=7.6Hz), 7.05 (2H, t, J=9Hz), 7.37 (2H, dd, J=5, 9Hz), 8.37

(1H, s)

MASS (APCI)(m/z): 296

Reference example 16

To a solution of N-(piperidin-4-yl)-N'-(4-fluorophenyl)urea (0.3 g) in tetrahydrofuran (4 ml) were added in turn N,N-dimethylaminopyridine (0.23 g) and 4-fluorobenzenesulfonyl chloride (0.25 g) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. The reaction mixture was taken up into a mixture of water and dichloromethane. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give N-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)-N'-(4-fluorophenyl)urea (0.468 g).

NMR (DMSO-d_6, δ): 1.3-1.6 (2H, m), 1.75-1.95 (2H, m), 2.45-2.7 (2H, m), 3.35-3.6 (3H, m), 6.14 (1H, d, J=7.5Hz), 7.03 (2H, t, J=9Hz), 7.34 (2H, dd, J=5, 9Hz), 7.50 (2H, t, J=9Hz), 7.75-7.95 (2H, m), 8.31 (1H, s)

MASS (APCI)(m/z): 396

Reference example 17

To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide (0.5 g) in dichloromethane (5 ml) were added pyridine (218 μl), dichloromethane (5 ml) and benzoyl chloride (290 μl) at ambient temperature. After stirring for 3.5 hours, water (5 ml) was poured into the mixture. An organic layer was separated, and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel, toluene:ethyl acetate = 1:1 to ethyl acetate). After rinse with diisopropyl ether, N-(1-benzoylpiperidin-4-yl)-4-fluorobenzamide (515 mg) was obtained.

NMR (DMSO-d_6, δ): 1.50 (2H, br s), 1.85 (2H, br s), 2.8-3.3 (2H, m), 3.61 (1H, m), 4.1 (1H, m), 4.35 (1H, m), 7.29 (2H, t, J=8.9Hz), 7.3-7.5 (5H, m), 7.92 (2H, dd, J=5.6, 8.9Hz), 8.34 (1H, d, J=7.9Hz)

MASS (APCI)(m/z): 327

Reference example 18

To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide (556 mg) in dichloromethane (5 ml) were added pivaloyl chloride (0.37 ml), pyridine (0.24 ml) and N,N-dimethylaminopyridine (25 mg) at ambient

temperature. After stirring for 1 day, the mixture was diluted with dichloromethane, and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After trituration with diisopropyl ether, N-(1-pivaloylpiperidin-4-yl)-4-fluorobenzamide (305 mg) was obtained.

NMR (DMSO-d_6, δ): 1.20 (9H, s), 1.41 (2H, m), 1.7-1.9 (2H, m), 2.91 (2H, br t, J=11.9Hz), 4.07 (1H, m), 4.27 (2H, br d, J=13.3Hz), 7.29 (2H, t, J=8.9Hz), 7.92 (2H, dd, J=5.5, 8.9Hz), 8.30 (1H, d, J=7.8Hz)

MASS (APCI)(m/z): 329

Reference example 19

To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide (556 mg) in dichloromethane (6 ml) were added cyclopropanecarboxylic acid (0.20 ml), 1-hydroxybenzotriazole (338 mg) and 1-etyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (480 mg) at ambient temperature. After stirring for 21 hours, the mixture was diluted with dichloromethane, and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After crystallization from diisopropyl ether, N-(1-cyclopropylcarbonylpiperidin-4-yl)-4-flurobenzamide (627 mg) was obtained.

NMR (DMSO-d_6, δ): 0.6-0.8 (4H, m), 1.2-1.6 (2H, m), 1.7-2.0 (2H, m), 1.85 (1H, m), 2.72 (1H, m), 3.21 (1H, m), 4.04 (1H, m), 4.30 (2H, m), 7.29 (2H, t, J=8.9Hz), 7.92 (2H, dd, J=5.6, 8.9Hz), 8.31 (1H, d, J=7.7Hz)

MASS (APCI)(m/z): 313

Reference example 20

1-tert-Butoxycarbonyl-4-(4-fluorophenylcarbamoyl)piperazine (0.30 g) was dissolved in a solution of hydrogen chloride in ethyl acetate (4N, 2 ml), and the solution was stirred at ambient temperature for 1 hour. The solvent was removed by evaporation under reduced pressure to give 1-(4-fluorophenylcarbamoyl)piperazine as a white powder, which was taken up into dichloromethane (3 ml), and to the mixture were added in turn pyridine (0.25 ml), 4-trifluoromethoxybenzoyl chloride (0.146 ml), and catalytic amount of N,N-dimethylaminopyridine. After stirring at ambient temperature for 12 hours, the mixture was washed in turn with hydrochloric acid (0.5N), aqueous sodium hydrogen carbonate, and brine, dried over magnesium

sulfate, and evaporated under reduced pressure. The residue was chromatographed on silica gel (50 ml) eluting with 0%-3% methanol in dichloromethane to give 1-(4-fluorophenylcarbamoyl)-4-(4-trifluoromethoxybenzoyl)piperazine (0.19 g).

NMR (DMSO-d_6, δ): 3.2-3.8 (8H, m), 7.08 (2H, t, J=9Hz), 7.35-7.5 (4H, m), 7.5-7.65 (2H, m)

MASS (LD)(m/z): 434.1

Reference example 21

The following compound was obtained by using methyl chloroformate as a reactive derivative at the carboxy group according to a similar manner to that of Reference example 20.

1-Methoxycarbonyl-4-(4-fluorophenylcarbamoyl)piperazine

NMR (DMSO-d_6, δ): 3.3-3.5 (8H, m), 3.62 (3H, s), 7.07 (2H, t, J=9Hz), 7.44 (2H, dd, J=5, 9Hz), 8.62 (1H, s)

MASS (APCI)(m/z): 282

Reference example 22

A mixture of N-acetylpiperidine-4-carboxylic acid (514 mg), 1-hydroxybenzotriazole (405 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (575 mg) and 4-fluoroaniline (284.2 ml) in dichloromethane (5 ml) was stirred for 18 hours at ambient temperature. The mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 40 ml, dichloromethane:methanol = 15:1). After trituration with diisopropyl ether, 1-acetyl-4-(4-fluorophenyl)carbamoylpiperidine (532 mg) was obtained.

NMR (DMSO-d_6, δ): 1.3-1.7 (2H, m), 1.8 (2H, m), 2.01 (3H, s), 2.5 (2H, m), 3.05 (1H, br t, J=10.6Hz), 3.87 (1H, br d, J=14.1Hz), 4.40 (1H, br d, J=13.1Hz), 7.12 (2H, t, J=8.9Hz), 7.61 (2H, dd, J=5.1, 9.1Hz), 9.96 (1H, s)

MASS (APCI)(m/z): 265

Reference example 23

A solution of 1-acetylpiperazine-4-sulfonyl chloride (0.91 g) in chloroform (10 ml) were added 4-fluoroaniline (0.38 ml) and triethylamine (0.56 ml) at ambient temperature. After stirring for 6 days, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml,

dichloromethane:methanol = 19:1). After rinse with diisopropyl ether, 1-acetyl-4-(4-fluorophenyl)sulfamoylpiperazine (716 mg) was obtained.

NMR ($CDCl_3$, δ): 1.97 (3H, s), 3.09 (4H, m), 3.37 (4H, m), 7.20 (4H, m), 10.00 (1H, s)

MASS (APCI)(m/z): 302

Reference example 24

To a solution of O-tert-butyl (1-acetylpiperidin-4-yl)carbamate (0.97 g) in N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.18 g) at ambient temperature. After stirring for 40 minutes, 4-fluorobenzyl bromide (0.6 ml) was added to the reaction mixture. After additional stirring for 4 hours, the reaction mixture was poured into a mixture of ethyl acetate (50 ml) and water (10 ml). An organic phase was separated and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, toluene:ethyl acetate = 1:1 to 1:2). After crystallization from diisopropyl ether and n-hexane, O-tert-butyl N-(4-fluorobenzyl)-N-(1-acetylpiperidin-4-yl)carbamate (922 mg) was obtained.

NMR (DMSO-d_6, δ): 1.35 (9H, br s), 1.3-1.8 (4H, m), 1.95 (3H, s), 2.3-2.6 (1H, m), 2.97 (1H, m), 3.80 (1H, br d, J=15.2Hz), 4.0 (1H, m), 4.32 (2H, s), 4.2-4.6 (1H, m), 7.0-7.4 (4H, m)

MASS (APCI)(m/z): 295

Reference example 25

To a solution of O-tert-butyl N-(4-fluorobenzyl)-N-(1-acetylpiperidin-4-yl)carbamate (0.5 g) in dichloromethane (5 ml) was added 4N hydrogen chloride in dioxane (5 ml). The reaction mixture was diluted with diisopropyl ether and the precipitates were collected by filtration. After drying under reduced pressure, 1-acetyl-4-(4-fluorobenzyl)-aminopiperidine hydrochloride (409 mg) was obtained.

NMR (DMSO-d_6+D_2O, δ): 1.54 (2H, m), 2.02 (3H, s), 2.0-2.3 (2H, m), 2.4-2.7 (1H, m), 3.04 (1H, br t, J=12.1Hz), 3.29 (1H, m), 3.9 (1H, m), 4,17 (2H, s), 4.44 (1H, br d, J=13.6Hz), 7.27 (2H, t, J=8.9Hz), 7.66 (2H, br t, J=6.8Hz)

MASS (APCI)(m/z): 251

Reference example 26

To a solution of N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide (529 mg) in N,N-dimethylformamide (5 ml) was added sodium hydride (0.1

g). After stirring for 45 minutes, methyl iodide (623 ml) was added to the solution. After stirring for 45 minutes, the mixture was diluted with ethyl acetate (100 ml) and water (50 ml). An organic phase was separated, and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After trituration with diisopropy ether, N-(1-acetylpiperidin-4-yl)-N-methyl-4-fluorobenzamide (248 mg) was obtained.

NMR (DMSO-d_6, δ): 1.65 (4H, m), 2.00 (3H, s), 2.78 (3H, s), 3.8 (1H, m), 4.4 (1H, m), 2.0-4.6 (3H, br m), 7.26 (2H, t, J=8.9Hz), 7.46 (2H, dd, J=5.6, 8.7Hz)

MASS (APCI)(m/z): 301

Reference example 27

A suspension of 1-acetylpiperazine (0.627 g), 2-chloro-4'-fluoroacetophenone (0.844 g), and potassium hydrogen carbonate (0.735 g) in acetonitrile (12 ml) was stirred at ambient temperature for 3 days. After removal of the solid by filtration, the filtrate was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (100 ml) eluting with 0%-5% methanol in dichloromethane. The objective compound of the free form was taken up into ethyl acetate (2 ml) and to the solution was added a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). The resulting precipitate was collected by filtration, washed with diisoporpyl ether, and dried in vacuo to give 1-acetyl-4-(4-fluorophenylcarbonylmethyl)-piperazine hydrochlride (1.47 g).

NMR (DMSO-d_6, δ): 2.06 (3H, s), 2.95-3.8 (6H, m), 3.9-4.15 (1H, m), 4.2-4.45 (1H, m), 5.13 (2H, s), 7.48 (2H, t, J=9Hz), 8.09 (2H, dd, J=5, 9Hz)

MASS (APCI)(m/z): 265

Industrial Applicability

An agent for expression of long-term potentiation of synaptic transmission comprising a compound having a brain somatostatin activation property of the present invention is effective for the prophylaxis and/or treatment of cerebral diseases such as dementia (e.g., senile dementia, Alzheimer's dementia, dementia associated with various diseases such as cerebral vascular dementia, cerebral post-traumatic dementia, dementia due to brain tumor, dementia due to chronic subdural hematoma, dementia due to normal pressure

hydrocephalus, post-meningitis dementia, Parkinson's disease type dementia, and the like), amnesia, manic-depressive psychosis, schizophrenia, Parkinson's disease, psychosomatic disease, and the like, particularly for the prophylaxis and/or treatment of dementia and amnesia. The present invention also relates to a screening method of an agent for the expression of long-term potentiation of synaptic transmission, which uses a somatostatin releasing property as an index. By using the present screening method, various compounds useful for the prophylaxis and/or treatment of the above-mentioned cerebral diseases can be selected.

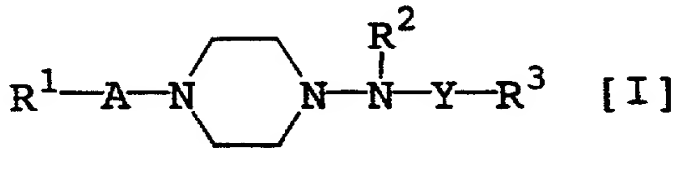
This invention is based on application No. 09/321,745 filed in the United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. An agent for expression of long-term potentiation of synaptic transmission, which comprises a compound having a brain somatostatin activation property as an active ingredient.

2. The agent for expression of long-term potentiation of synaptic transmission of claim 1, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

3. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [I]:



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

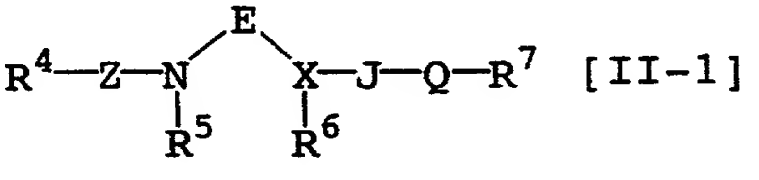
R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, $-SO_2-$ or lower alkylene, and

Y is -CO-, $-SO_2-$ or -CONH-,

or pharmaceutically acceptable salts thereof.

4. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [II-1]:



[II-1]

wherein

R^4 is acyl,

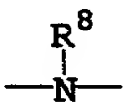
R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or $-SO_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or



wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

Q is $-CH_2-$, -CO-, $-SO_2-$ or -N=CH-, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

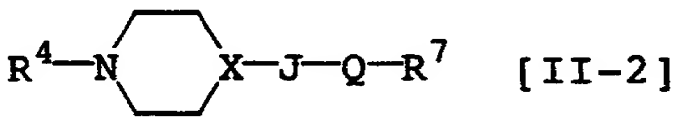
provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or $-SO_2-$, or

2) J is lower alkylene,

or pharmaceutically acceptable salts thereof.

5. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [II-2]:



[II-2]

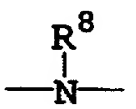
wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or



wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

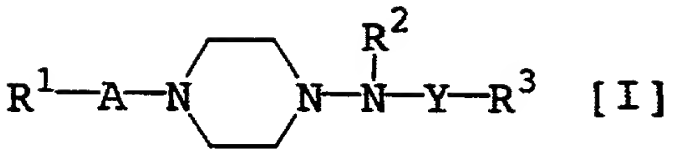
6. The agent for expression of long-term potentiation of synaptic transmission of any of claim 1 to claim 5, which is an agent for the prophylaxis or treatment of cerebral diseases.

7. The agent for expression of long-term potentiation of synaptic transmission of claim 6, which is an agent for the prophylaxis or treatment of dementia or amnesia.

8. A method for expressing long-term potentiation of synaptic transmission, comprising administering an effective amount of a compound having a brain somatostatin activation property.

9. The method for expressing long-term potentiation of synaptic transmission of claim 8, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

10. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [I]:



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

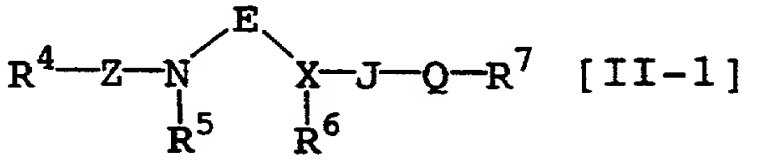
R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, $-SO_2-$ or lower alkylene, and

Y is -CO-, $-SO_2-$ or -CONH-,

or pharmaceutically acceptable salts thereof.

11. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [II-1]:



[II-1]

wherein

R^4 is acyl,

R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or $-SO_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

Q is $-CH_2-$, $-CO-$, $-SO_2-$ or $-N=CH-$, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

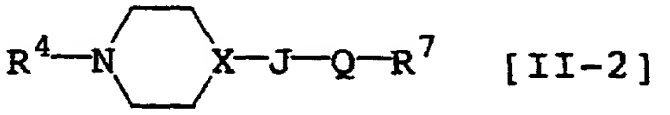
provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, $-CO-$ or $-SO_2-$, or

2) J is lower alkylene,

or pharmaceutically acceptable salts thereof.

12. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [II-2]:



[II-2]

wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene,

or pharmaceutically acceptable salts thereof.

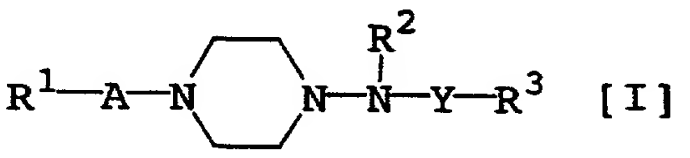
13. The method for expressing long-term potentiation of synaptic transmission of any of claim 8 to claim 12, which is a method for the prophylaxis or treatment of cerebral diseases.

14. The method for expressing long-term potentiation of synaptic transmission of claim 13, which is a method for the prophylaxis and/or treatment of dementia or amnesia.

15. Use of a compound having a brain somatostatin activation property for the production of an agent for the expression of long-term potentiation of synaptic transmission.

16. The use of a compound having a brain somatostatin activation property according to claim 15, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

17. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula [I]:



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

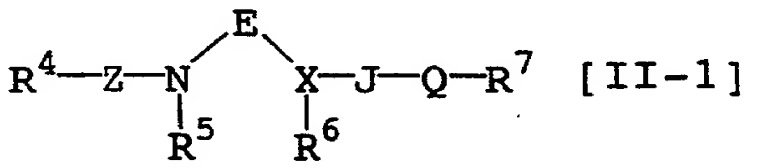
R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, $-SO_2-$ or lower alkylene, and

Y is -CO-, $-SO_2-$ or -CONH-,

or pharmaceutically acceptable salts thereof.

18. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula [II-1]:



[II-1]

wherein

R^4 is acyl,

R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or $-SO_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

Q is $-CH_2-$, -CO-, $-SO_2-$ or -N=CH-, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

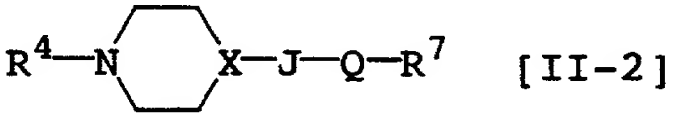
provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or $-SO_2-$, or

2) J is lower alkylene,

or pharmaceutically acceptable salts thereof.

19. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula [II-2]:



[II-2]

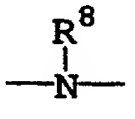
wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or



wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

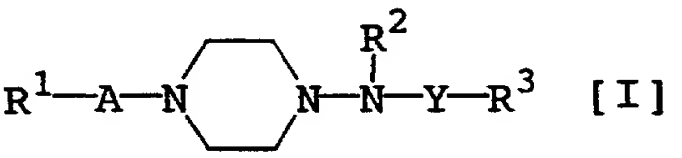
20. The use of a compound having a brain somatostatin activation property according to any of claim 15 to claim 19, which is for the production of an agent for the prophylaxis and/or treatment of cerebral diseases.

21. The use of a compound having a brain somatostatin activation property according to claim 20, which is for the production of an agent for the prophylaxis and/or treatment of dementia or amnesia.

22. A pharmaceutical composition for expression of long-term potentiation of synaptic transmission, which comprises a compound having a brain somatostatin activation property, and a pharmaceutically acceptable carrier or excipient.

23. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

24. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein the compound has the following formula [I]:



[I]

wherein

R^1 is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R^2 is hydrogen atom or lower alkyl,

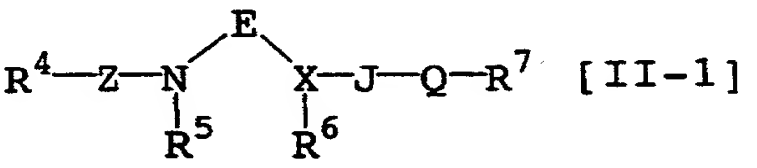
R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, $-SO_2-$ or lower alkylene, and

Y is -CO-, $-SO_2-$ or -CONH-,

or pharmaceutically acceptable salts thereof.

25. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein the compound has the following formula [II-1]:



[II-1]

wherein

R^4 is acyl,

R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino,

cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

Z is a single bond, -CO- or $-SO_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

Q is $-CH_2-$, -CO-, $-SO_2-$ or -N=CH-, and

R^5 and R^6 are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

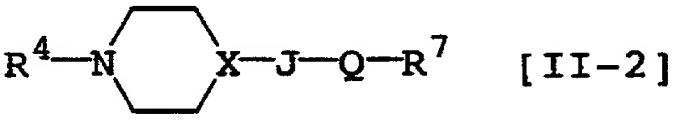
provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or $-SO_2-$, or

2) J is lower alkylene,

or pharmaceutically acceptable salts thereof.

26. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein the compound has the following formula [II-2]:



[II-2]

wherein

R^4 is acyl,

R^7 is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

J is a single bond, lower alkylene or

wherein R^8 is hydrogen, lower alkyl or an N-protective group,

Q is $-CH_2-$, $-CO-$ or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

27. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of any of claim 22 to claim 26, which is a pharmaceutical composition for the prophylaxis or treatment of cerebral diseases.

28. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 27, which is a pharmaceutical composition for the prophylaxis or treatment of dementia or amnesia.

29. A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises using a somatostatin releasing action as an index.

30. The screening method of claim 29, which is a screening method of an anti-dementia agent or anti-amnesia agent.

31. A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises stimulating hippocampal slices, bringing a hippocampal slice into contact with a test compound, measuring an amount of somatostatin released from the hippocampal slice and/or a release time thereof, measuring an amount of somatostatin released from a hippocampal slice and/or a release time thereof in the absence of a contact with the test compound, and comparing the amounts and/or the times to calculate the amount of somatostatin released from the hippocampal slice and/or the release

time thereof caused by the contact with the test compound.

32. The screening method according to claim 31, which is a screening method of an anti-dementia agent or anti-amnesia agent.

33. The agent for expression of long-term potentiation of synaptic transmission of claim 1, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

34. The method for expressing long-term potentiation of synaptic transmission according to claim 8, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

35. The use of a compound having a brain somatostatin activation property according to claim 15, wherein the compound having the brain somatostatin activation property is obtained by the screening method of any of claim 29 to claim 32.

36. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

37. A commercial package comprising the pharmaceutical composition for expression of long-term potentiation of synaptic transmission of any of claim 22 to claim 28 or claim 36 and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition can or should be used for expression of long-term potentiation of synaptic transmission.

38. A compound selected by the screening method described in any of claim 29 to claim 32.

FIG.1

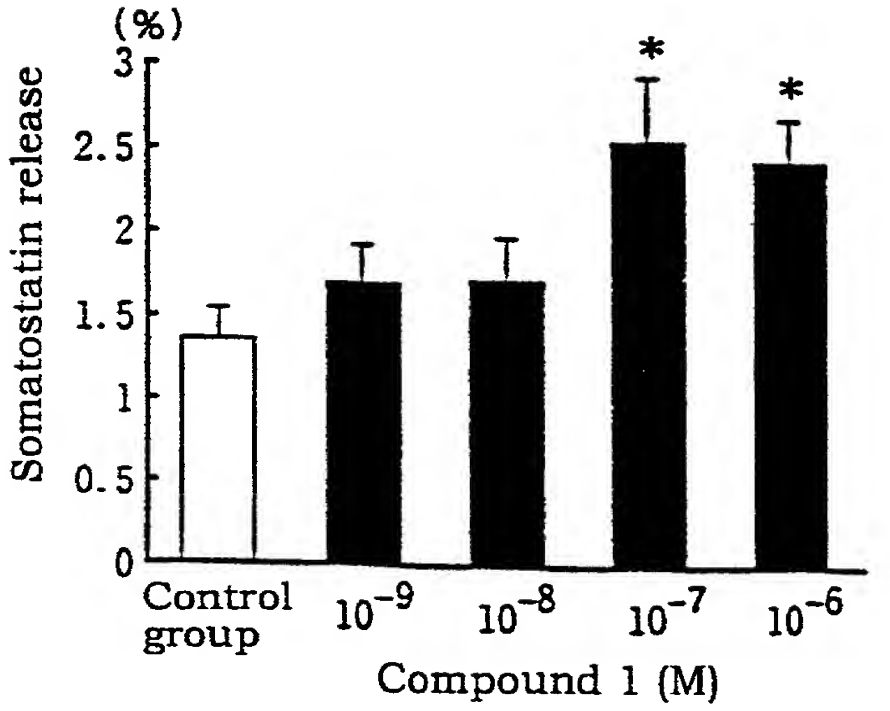

(%)
Somatostatin release
3
2.5
2
1.5
1
0.5
0
*
*
Control group
10^{-9}
10^{-8}
10^{-7}
10^{-6}
Compound 1 (M)

FIG.2

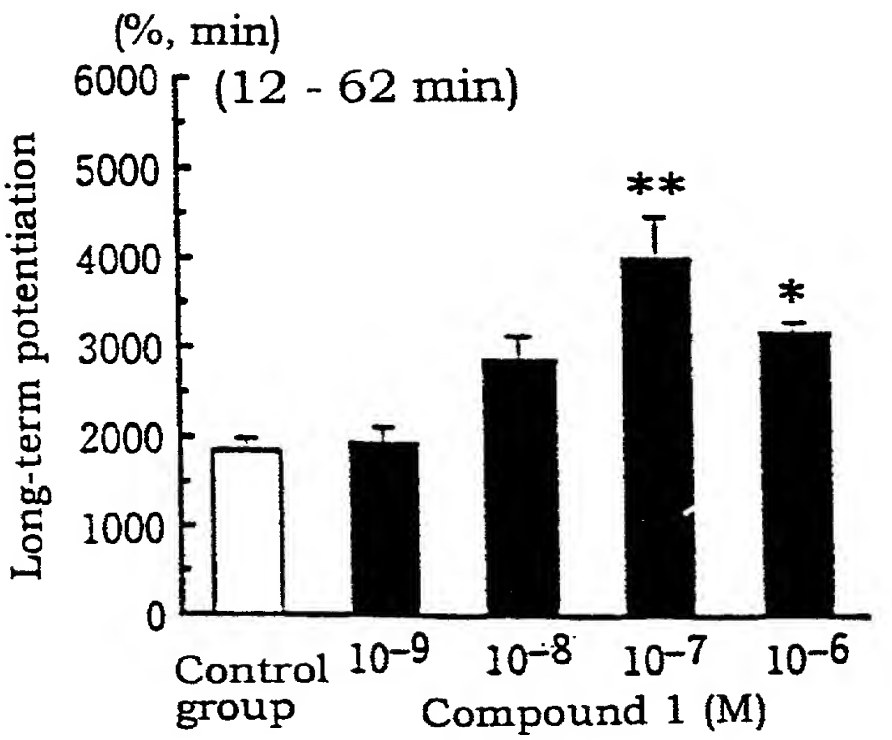


FIG.3

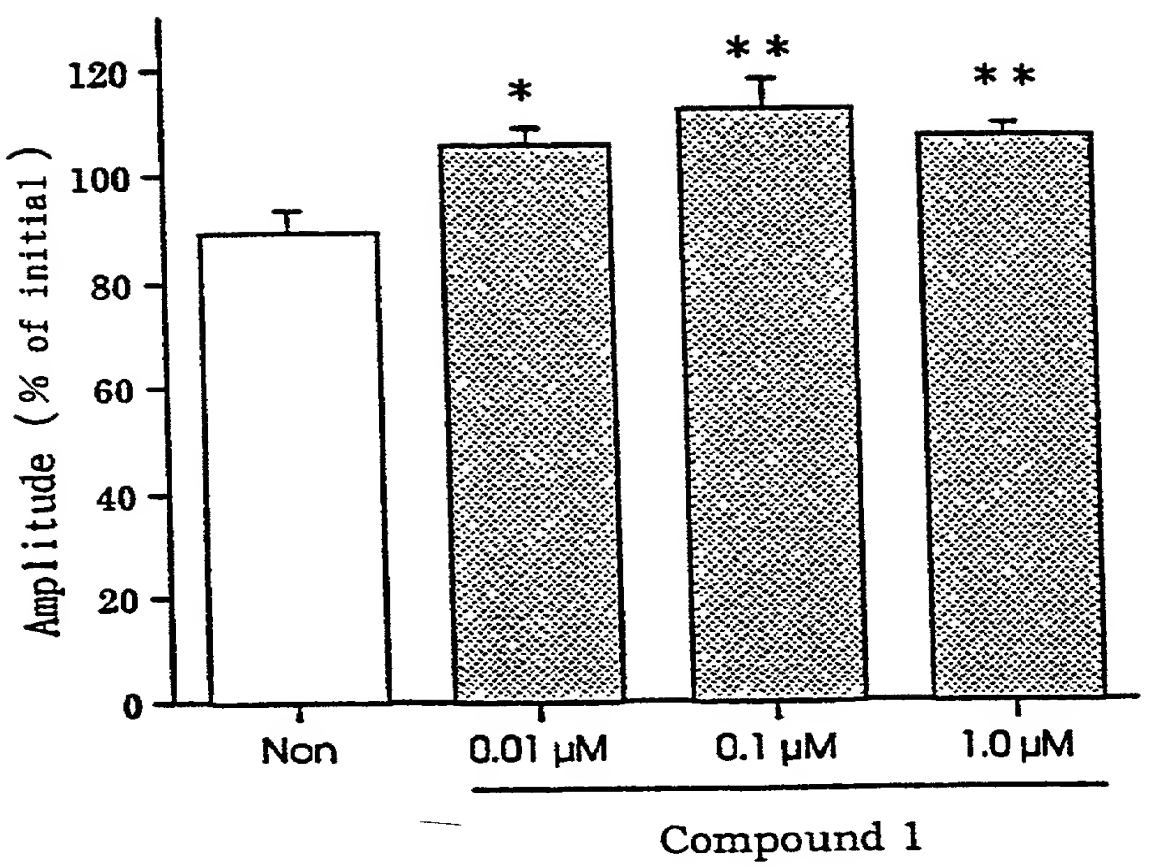
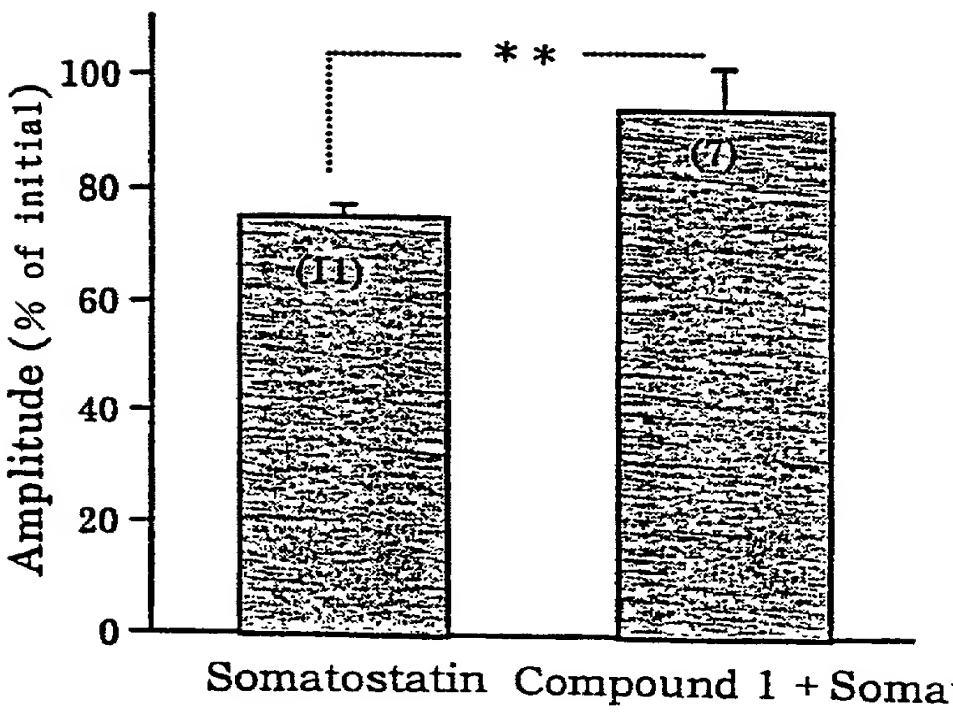


FIG.4



Declaration, Power of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AGENT FOR EXPRESSION OF LONG-TERM POTENTIATION OF SYNAPTIC TRANSMISSION COMPRISING COMPOUND HAVING BRAIN SOMATOSTATIN ACTIVATION PROPERTY

the specification of which

☒ is attached hereto.
☐ was filed on _____ as
Application Serial No. _____
and amended on _____ .
☒ was filed as PCT international application
Number PCT/JP00/03334
on May 24, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 1 19(a)-(d) or § 365(b,) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
09/321,745	May 28, 1999	pending
PCT/JP00/03334	May 24, 2000	pending

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Timothy R. Schwart, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; Richard L. Chinn, Registration Number 34,305; Steven E. Lipman, Registration Number 30,011; Carl E. Schlier, Registration Number 34,426; James J. Kulbaski, Registration Number 34,648; Catherine B. Richardson, Registration Number 39,007; Richard A. Neifeld, Registration Number 35,299; J. Derek Mason, Registration Number 35,270; and Jacques M. Dulin, Registration Number 24,067; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Tide 18 of the United States Code and that such willfull false statements may jeapordize the validity of the application or any patent issuing thereon.

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